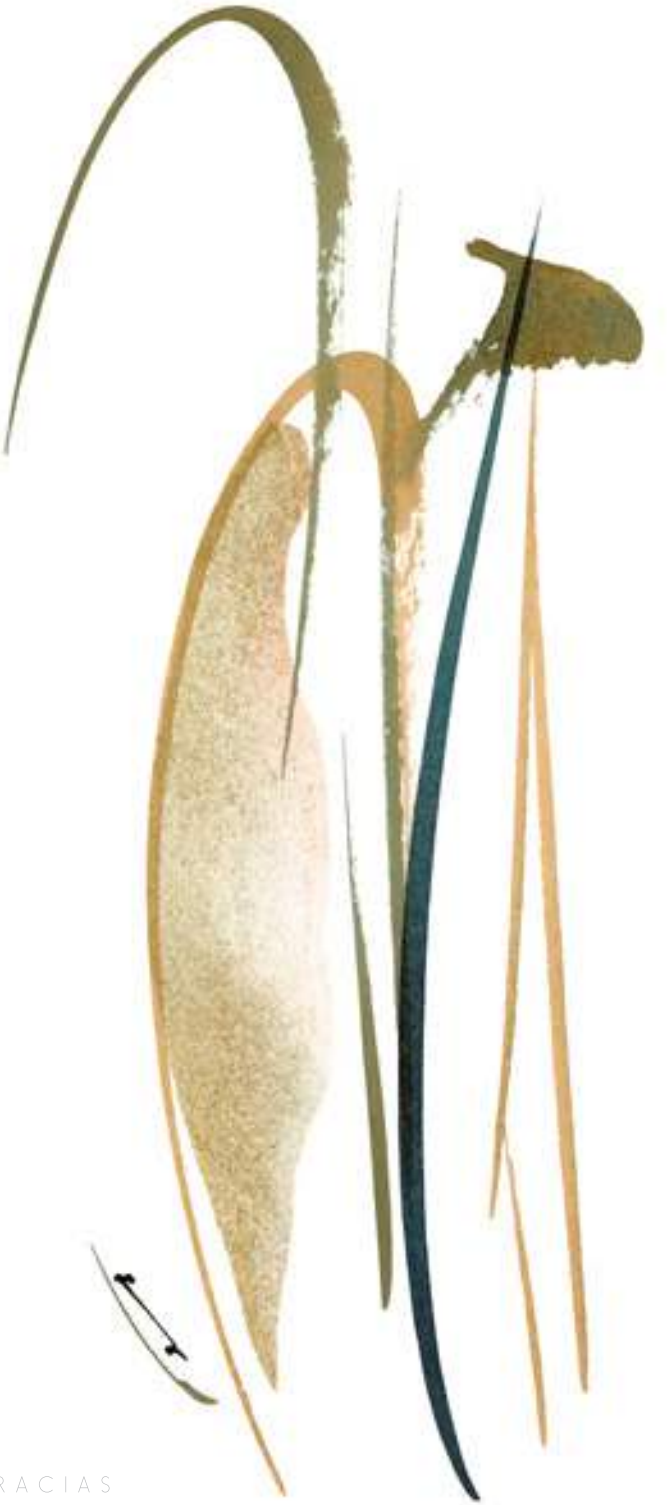
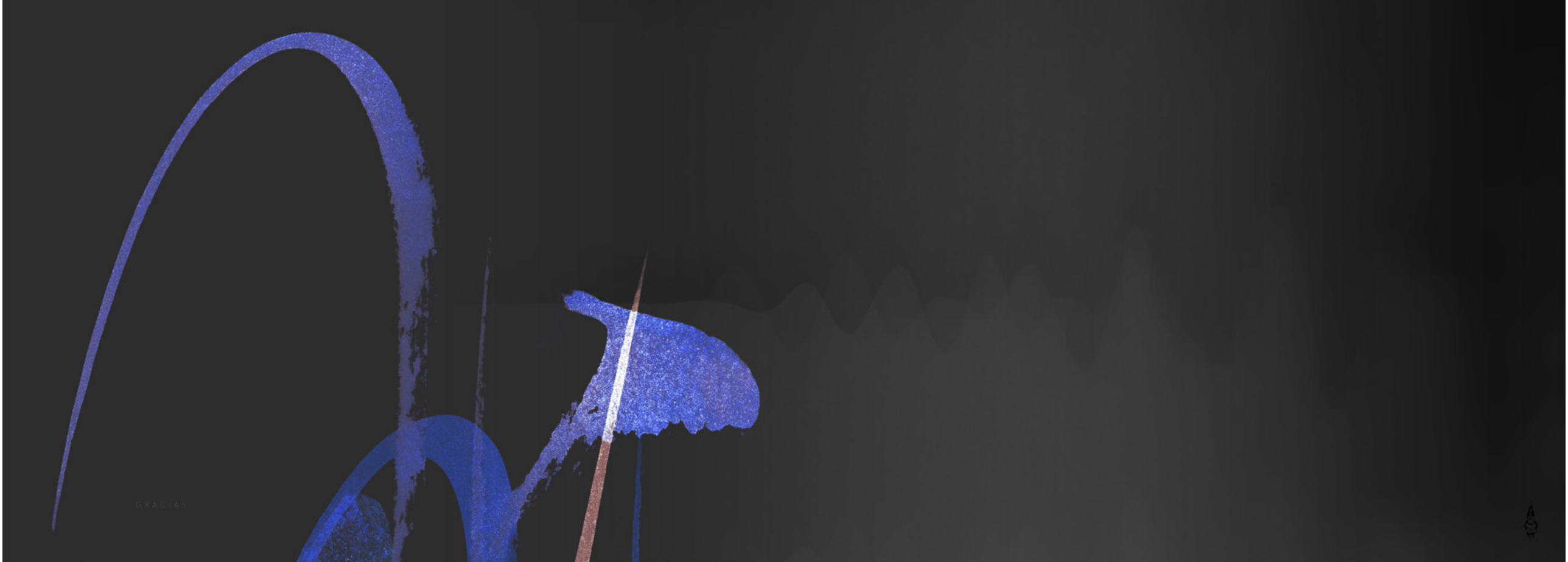
ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION & ACCELERATED REHABILITATION. HAMSTRING TENDONS, REMODELLING AND OSTEOARTHRITIS

Rob P. A. Janssen



GRACIAS


GRACIAS

STELLINGEN

I. Doelstelling van 'accelerated brace-free rehabilitation' bij een voorste kruisbandreconstructie is niet een sneller 'return to sports', maar een volledig symmetrische kniefunctie en belastbaarheid vanaf het moment van het letsel *(dit proefschrift)*

II. Hamstringpezen groeien weer aan na te zijn verwijderd ten behoeve van een voorste kruisbandreconstructie *(dit proefschrift)*

III. Een voorste kruisbandreconstructie beschermt niet tegen gonartrose op de lange termijn *(dit proefschrift)*

IV. De terugkeer naar onbeperkt sporten 4-6 maanden na een voorste kruisbandreconstructie is niet verstandig gezien het tijdsverloop van genezing van het kruisbandtransplantaat *(dit proefschrift)*

V. Anterior cruciate ligament surgery is not for all patients, nor for all surgeons *(Lars Engebretsen)*

VI. Whenever you are having your anatomy sessions, pay particular attention, because orthopaedics is all about anatomy, plus a little common sense *(Jack Hughston)*

VII. Een decentrale selectie voor de studie geneeskunde zal leiden tot een nieuwe man-vrouw verhouding onder artsen

VIII. Voetbalvrouwen lopen minder risico op een versleten knie dan voetballende vrouwen

IX. De congruentie tussen vorm, inhoud en praktijkvoering draagt bij aan het succes van een professionele medische website & sociale media

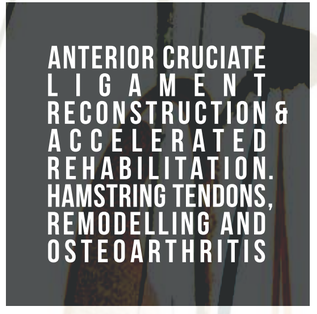
X. You have to play a long time before you can play like yourself *(Miles Davis)*

XI. De verdediging van een proefschrift is net als een zwemdiploma: als je "op mag" haal je het altijd *(Daan Janssen)*

ROB P.A. JANSSEN 2016

UITNODIGING

voor het bijwonen van de openbare verdediging van het proefschrift



26 MEI 2016 om **14:00**
AULA UNIVERSITEIT MAASTRICHT

Minderbroedersberg 4-6 te Maastricht
Receptie ter plaatse na afloop

ROB P.A. JANSSEN

PARANIMFEN

Roel Schins
Ruud Janssen

promotierpajanssen@gmail.com

RPA 20 16 PhD

GRACIAS

Anterior Cruciate Ligament Reconstruction &
Accelerated Rehabilitation.
Hamstring Tendons, Remodelling and Osteoarthritis

Rob P.A. Janssen

Colophon

Author:	Rob P.A. Janssen
Art work and design:	Rhea Strik, Tayfun van Zantvoort
Typography/Layout:	Lisa van der Mierden
Printing:	Coers & Roest
ISBN/EAN:	978-90-9029644-9

The publication of this PhD thesis was kindly supported by:
Stichting A.A. Onderzoek en Wetenschap
Wetenschapfonds Máxima Medisch Centrum
Nederlandse Vereniging voor Arthroscopie
Nederlandse Orthopaedische Vereniging

Anterior Cruciate Ligament Reconstruction & Accelerated Rehabilitation. Hamstring Tendons, Remodelling and Osteoarthritis

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan
de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. L.L.G. Soete
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 26 mei 2016 om 14:00 uur

door

Robertus Paulus Augustinus Janssen

Promotiecommissie

Promotor Prof.dr. L.W. van Rhijn
Copromotor Dr. J.B.A. van Mourik

Beoordelingscommissie
Prof.dr. R.A. de Bie (voorzitter)
Prof.dr. R.L. Diercks (Rijksuniversiteit Groningen)
Prof.dr. I.C. Heyligers
Prof.dr. G.M.M.J. Kerkhoffs (Universiteit van Amsterdam)
Prof.dr. N.L.U. van Meeteren

Preface

During my orthopaedic residency (1998-2002), I witnessed the transition from a two-incision anterior cruciate ligament (ACL) reconstruction with patellar tendon autograft and brace-rehabilitation to the single-incision hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. These were very interesting times, for clinical evidence for the new technique and rehabilitation was limited. Many controversies on graft choice, surgical technique and rehabilitation were frequently debated between staff and residents in clinical rounds and scientific meetings. Jan van Mourik MD, PhD, orthopaedic residency programme director as well as knee surgeons Harm Sala MD and Arthur Lim MD, PhD stimulated my enthusiasm for scientific research on ACL reconstruction. I am most grateful to all of them, as these ideas laid the foundation for this PhD research. The prospective study on long-term results and osteoarthritis after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation started in this period.

In 2005, I had the honour of being chairman of an international ACL Study Day in Amsterdam, The Netherlands. Among the distinguished faculty were Prof. Stephen Howell MD (USA); Prof. Markus Arnold MD, PhD (Switzerland) and Michael Rousseaux MD (Belgium). The discussions focused on graft fixation strength and stiffness, principles of tibial and femoral tunnel placement, iso-anatomical tunnel positions and biomechanical implications, graft impingement, tunnel widening and aggressive brace-free rehabilitation after hamstring tendon ACL reconstruction. This meeting enhanced new research ideas and engaged the prospective studies on harvested hamstring tendon size, tendon regeneration after hamstring harvest and complications related to hardware after ACL reconstruction with accelerated brace-free rehabilitation. These studies have taught me the value of meticulous documentation of patient-related outcome.

The collaboration with the team led by Prof. Andreas Weiler MD, PhD and Sven Scheffler MD, PhD in 2009 was a once in a lifetime opportunity to analyse in vivo human hamstring tendon autograft remodelling after ACL reconstruction with standardized accelerated brace-free rehabilitation. At the Charité Center for Musculoskeletal Surgery (Berlin, Germany), we were fortunate to perform the same immunostaining analyses as were done in previous animal studies on which ACL rehabilitation protocols have been based worldwide. On behalf of my co-authors, I am proud that these studies have had considerable impact in sports medicine and ACL rehabilitation.

In more recent years, vivid out of the box discussions on ACL reconstruction and rehabilitation with Prof. Lodewijk van Rhijn MD, PhD, Jan van Mourik MD, PhD and the appraisal of systematic reviews by Max Reijman PhD led to the final reviews on accelerated brace-free rehabilitation after ACL reconstruction. At the recent 25th Anniversary NVA Congress (Nederlandse Vereniging voor Arthroscopie - Dutch Arthroscopy Society), a scientific session on tendon pathology has inspired me to think of new research modalities for ACL graft remodelling in the future.

Combining science and clinical practice is like eating "Surf & Turf." They may seem different, but combining them raises the level of excellence. Combining scientific interest and clinical implications in daily practice has fascinated me for many years. I feel fortunate to be able to focus on knee disorders in both research and clinical practice at the Orthopaedic Centre Máxima Eindhoven, The Netherlands. I have been able to share my enthusiasm for research with my co-authors and orthopaedic residents as orthopaedic residency programme deputy director. Their critical views reminded me of the vivid 1990's discussions on ACL developments during my own residency.

This "Surf & Turf" knee experience has led to many rewarding projects: chapters in international ACL books, worldwide lectures and faculty memberships in annual international knee ligament courses. Inspiration never stops. A PhD thesis makes you realize how much still needs to be investigated...

"Je leert net zo lang totdat al je vingers even lang zijn, behalve als je in een houtzagerij werkt"
(W.A. & J.M. Janssen)

INTRODUCTION

Injuries of the anterior cruciate ligament (ACL) frequently occur in cutting and pivoting sports such as football (soccer), field hockey, indoor sports, alpine skiing and tennis.[33, 62] In Scandinavia, 40–50% of all ACL ruptures occur during football.[19] Women suffer ACL ruptures more frequently than men.[1, 33, 62] The overall incidence of ACL injury is 78 per 100.000 persons.[49] The group between 15–39 years old, which could be described as the group at risk, shows an incidence of 85–91 in 100.000 people per year.[19]

Spontaneous healing of a ruptured ACL is rare.[4, 12, 17, 28, 39] Patients with an ACL rupture may experience knee instability and are at risk for concomitant injuries of menisci, cartilage and collateral ligaments.[33, 43] Functional instability of the knee can be treated by ACL reconstruction, which ranks number 6 of most performed orthopaedic operations.[49]
In 2013, the incidence of ACL reconstructions in the Netherlands is estimated at 46 in 100.000 people per year, compared to 43.5 in 100.000 people per year in the USA.[43, 65] The incidence of ACL reconstructions increases, particularly in women as well as patients younger than 20 years and those 40 years and older.[43]

Hamstring tendons continue to gain in popularity as graft source for ACL reconstruction.[47] In 2012, 95% of the primary ACL reconstructions in Sweden were performed with hamstring tendon autografts.[40] The success rate varies between 55–95% depending on surgical technique and level of sports activity after reconstruction.[3, 19, 22, 38, 47, 49, 53, 66, 70]

Historical perspective
Macey[42] originally described the use of a hamstring graft in 1939 much as it is used today.[45] Zarins and Rowe[71] popularized the use of hamstring tendons when they published their results of a semitendinosus tendon reconstruction modified by adding an extra-articular MacIntosh II procedure. Their combined reconstruction was widely used in the 1980's and gave excellent stability. However, the required arthrotomy and significant dissection frequently resulted in pain and loss of knee motion.[45]
Due to technical advances in the same decade, arthroscopic techniques and instrumentation became available. As surgeons began to gain greater facility with the arthroscope, they sought modifications to the existing reconstructions that would allow them to perform isolated intra-articular ACL reconstructions.[45]

In the 1980's, the bone-patellar tendon-bone autograft was the gold standard for ACL reconstruction. Animal research suggested that intra-articular patellar tendon ACL grafts underwent a remodelling process. This healing process included a phase in which the graft was partially necrotic and therefore needed protection.[13, 16, 29, 55] This protection against excessive stress on the reconstructed graft required wearing a knee brace, limited weight-bearing, restricted range of motion and avoidance of early full terminal extension.[13] Despite good ligamentous stability, common rehabilitation problems occurred including knee stiffness, lack of full extension, anterior knee pain, muscle weakness and knee crepitus.[13, 58]

Shelbourne et al.[58] noticed that noncompliant patients (with full range of motion, normal gait and resuming normal activities of daily living earlier than prescribed) achieved faster return of strength and a quicker return to activities without graft failure. They adapted their rehabilitation to obtain full range of motion preoperatively with immediate weight-bearing, full leg extension and knee flexion past 90° after ACL reconstruction.[58] These evolutionary changes became the basis of current accelerated brace-free rehabilitation protocols with a progressive scheme that allows patients to advance as they achieve quantifiable goals.[38, 50, 58, 60, 64, 68, 69]
Rehabilitation starts at the time of injury and includes aggressive swelling reduction, hyperextension exercises, gait training and mental preparation preoperatively.[56, 58] Regardless of the graft source, rehabilitation after ACL reconstruction must first strive to achieve full symmetrical knee range of motion before aggressive strengthening is started.[58] After quadriceps-strengthening goals are reached, patients can shift to sport-specific exercises and return to sports.[8, 57, 58, 60]

In the 1990's, advances in arthroscopic guides and better graft fixation techniques allowed single-incision ACL reconstruction with intra-articular drilling of the femoral tunnel.[27, 45] The 1990's were the decade of autograft transition from patellar tendon to hamstring tendon in the Netherlands. Among others, Rosenberg & Deffner and Howell et al. argued that hamstring tendons were the preferred graft choice for ACL reconstruction because of superior strength, larger cross-sectional area for footprint recreation, graft tunnel conformity, biological incorporation, stability, and less donor site morbidity and anterior knee pain compared to bone-patellar tendon-bone autografts.[24–27, 54] Return to sports was allowed at 4–6 months after ACL reconstruction.[25] As a result, their surgical reconstruction techniques became popular in combination with accelerated brace-free rehabilitation protocols and are still widely used today.

Research perspective
Hamstring tendon autograft ACL reconstructions have a 25-year track record. The surgical techniques have been improved to better restore anatomy and biomechanics of the knee. Various single- and double-bundle reconstruction techniques require specific hamstring tendon dimensions. In light of these developments, prediction of hamstring tendon length and diameter by anthropometric parameters could be useful in preoperative planning. It could also reduce the need for expensive allografts in complex knee surgery and increases the quality of ligament reconstructions with regard to graft rupture and postoperative stability.[5, 9, 11, 15, 35, 41, 48, 52, 61] Furthermore, prediction of hamstring tendon size allows knee ligament reconstructions to be performed with greater confidence in countries where allografts are not available.

Regeneration of hamstring tendons in the upper leg, after harvest for ACL reconstruction, has been reported in mostly retrospective research.[32] Prospective MRI studies, comparing the operated- and contralateral leg, could document tendon regeneration in relation to muscle cross-sectional area and muscle retraction. In case of tendon regeneration, the correlation between tendon regeneration and isokinetic flexion strength may be analysed. This knowledge might allow more individualized strength training in ACL rehabilitation.

Successful ACL reconstruction requires understanding of several factors: anatomical graft placement, mechanical properties of the selected graft tissue, mechanical behaviour and fixation strength of fixation materials as well as the biological processes that occur during graft healing.[29] They influence directly the mechanical properties of the knee joint after ACL reconstruction and, therefore, determine the rehabilitation and time course until normal function of the knee joint can be expected.[30, 31]

After surgery, graft healing is characterized by a remodelling process.[29, 31, 44, 46] During this period, the graft will undergo changes, becoming morphologically similar to intact ligament tissue.[18, 29, 31, 55] Remodelling takes 6-12 months in animal models.[55] Data from these animal studies has been extrapolated to current human ACL rehabilitation protocols.[30] However, little is known about remodelling and its duration in humans. Histological analysis at various time frames after ACL reconstruction is necessary to analyse human hamstring tendon autograft remodelling. Differences in remodelling between animals and humans may lead to new ACL rehabilitation protocols.

In recent decades, there was little agreement among surgeons regarding postoperative treatment after ACL reconstruction.[62] Advantages of accelerated brace-free rehabilitation are earlier normal knee function and the ability to return to even most strenuous activities after primary ACL reconstruction at 6 months.[2, 7, 18, 24, 29, 59] However, some authors found that early return to vigorous physical activity may increase knee laxity.[30] Current views suggest that time-related thinking in return to sports is not correct and individualized ACL rehabilitation is recommended.[36]

It is agreed that ACL graft healing can only progress if mechanical loading occurs: however, the most adequate magnitude at varying phases of healing is still not clarified.[29] A major challenge in postoperative rehabilitation after ACL reconstruction is optimizing the balance between muscular strengthening exercises and loading of the graft, to stimulate graft cells to produce cellular and extracellular components for preservation of graft stability, without compromising graft integrity, which might result into an early stretch-out of the ACL reconstruction.[6, 7, 29, 55, 67]

Despite extensive research on ACL reconstruction and rehabilitation, optimal balance of graft loading and graft healing in the various rehabilitation phases after ACL reconstruction requires further research. Knowledge about the duration of the remodelling process of ACL grafts might improve rehabilitation protocols and facilitates the development of criterion-based assessments to determine safe return to sports.[2, 29-31, 34]

Short- to midterm clinical outcome after ACL reconstruction is often reported in terms of patient satisfaction, knee laxity, graft rerupture rate and return to sports. These may be documented by patient-reported outcome measures and validated outcome scores such as KOOS (Knee injury and Osteoarthritis Outcome Score), Tegner-, Lysholm- and IKDC- (International Knee Documentation Committee) scores.[10, 20, 21, 23, 37, 63] Many variables influence the outcome of ACL reconstruction. Predictors of activity level should control for patients' preoperative activity because this is a strong predictor of future activity.[14]

ACL reconstruction does not prevent knee osteoarthritis.[51] Long-term results after ACL reconstruction are important to analyse predictors of osteoarthritis. Øiestad et al. proposed guidelines for future research on osteoarthritis based on their systematic review.[51]

Aim and outline of thesis
The aim of this thesis is to gain insights into the characteristics and biology of hamstring tendons as well as long-term clinical outcome after hamstring tendon autograft ACL reconstruction with accelerated brace-free rehabilitation. The same surgical technique and standardized accelerated rehabilitation protocol were used in all clinical studies of this thesis.
To answer the research questions related to the aim of the thesis, I have first presented a systematic literature review of the current knowledge on accelerated brace-free rehabilitation after hamstring tendon ACL reconstruction (**Chapter 2**). In the next four chapters, I have chosen to deepen the knowledge on hamstring autografts used for ACL reconstruction. These chapters encompass the central part of the thesis and focus on hamstring tendon graft size, regeneration, biology and remodelling of human hamstring tendon ACL grafts. The aim of **Chapter 3** is to evaluate preoperative prediction of hamstring tendon length and diameter by anthropometric parameters in a consecutive series of 725 Caucasian patients. **Chapter 4** describes hamstring tendon regeneration in the upper leg after harvest for ACL reconstruction and the contribution of regenerated tendons to isokinetic hamstring strength. The biopsy study of 67 patients presented in **Chapter 5** illustrates the histology and morphology of hamstring autograft remodelling in various phases after successful ACL reconstruction with standardized accelerated brace-free rehabilitation. **Chapter 6** describes the current knowledge on hamstring ACL graft remodelling. A comparison is made between human and animal data to discuss consequences for rehabilitation. Finally, I present the long-term clinical outcome in a 10-year prospective study of 100 patients in **Chapter 7**. Predictors of knee osteoarthritis were determined by univariate and multivariate regression analysis. **Chapter 8** discusses the accelerated rehabilitation after ACL reconstruction, return to sports in light of graft healing and new horizons for future research on graft remodelling and rehabilitation.

References

1. Ageberg E, Forssblad M, Herbertsson P, Roos EM (2010) Sex differences in patient-reported outcomes after anterior cruciate ligament reconstruction: data from the Swedish knee ligament register. Am J Sports Med 38(7):1334–1342

2. Andersson D, Samuelsson K, Karlsson J (2009) Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials. Arthroscopy 25(6):653–685

3. Ardern CL, Taylor NF, Feller JA, Webster KE (2014) Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 48(21):1543–1552

4. Arts SJ, Polak MP, Janssen RP (2015) Anterior cruciate ligament regeneration in an 8-year-old patient. J Knee Surg Rep:1–4

5. Barrett GR, Luber K, Replogle WH, Manley JL (2010) Allograft anterior cruciate ligament reconstruction in the young, active patient: Tegner activity level and failure rate. Arthroscopy 26(12):1593–1601

6. Beynnon BD, Fleming BC, Johnson RJ, Nichols CE, Renstrom PE, Pope MH (1995) Anterior cruciate ligament strain behavior during rehabilitation exercises in vivo... presented at the joint meeting of the International Society of the Knee/International Arthroscopy Association of America, Copenhagen, Denmark, June 27, 1993. Am J Sports Med 23(1):24–34

7. Beynnon BD, Johnson RJ, Naud S, Fleming BC, Abate JA, Brattbakk B, Nichols CE (2011) Accelerated versus nonaccelerated rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind investigation evaluating knee joint laxity using roentgen stereophotogrammetric analysis. Am J Sports Med 39(12):2536–2548

8. Biggs A, Jenkins WL, Urch SE, Shelbourne KD (2009) Rehabilitation for patients following ACL reconstruction: a knee symmetry model. N Am J Sports Phys Ther 4(1):2–12

9. Borchers JR, Pedroza A, Kaeding C (2009) Activity level and graft type as risk factors for anterior cruciate ligament graft failure: a case-control study. Am J Sports Med 37(12):2362–2367

10. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR (2009) The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. Am J Sports Med 37(5):890–897

11. Cooper MT, Kaeding C (2010) Comparison of the hospital cost of autograft versus allograft soft-tissue anterior cruciate ligament reconstructions. Arthroscopy26(11): 1478–1482

12. Costa-Paz M, Ayerza MA, Tanoira I, Astoul J, Muscolo DL (2012) Spontaneous healing in complete ACL ruptures: a clinical and MRI study. Clin Orthop Relat Res 470(4):979–985

13. De Carlo M, Klootwyk TE, Shelbourne KD (1997) ACL surgery and accelerated rehabilitation: revisited. J Sport Rehabil 6(2):144–156

14. Dunn WR, Spindler KP, Consortium M (2010) Predictors of activity level 2 years after anterior cruciate ligament reconstruction (ACLR): a Multicenter Orthopaedic Outcomes Network (MOON) ACLR cohort study. Am J Sports Med 38(10):2040–2050

15. Engelman GH, Carry PM, Hitt KG, Polousky JD, Vidal AF (2014) Comparison of allograft versus autograft anterior cruciate ligament reconstruction graft survival in an active adolescent cohort. Am J Sports Med 42(10):2311–2318

16. Escamilla RF, Macleod TD, Wilk KE, Paulos L, Andrews JR (2012) Anterior cruciate ligament strain and tensile forces for weight-bearing and non-weight-bearing exercises: A guide to exercise selection. J Orthop & Sports Phys Ther 42(3):208–220

17. Fujimoto E, Sumen Y, Ochi M, Ikuta Y (2002) Spontaneous healing of acute anterior cruciate ligament (ACL) injuries – conservative treatment using an extension block soft brace without anterior stabilization. Arch Orthop Trauma Surg 122(4):212–216

18. Fukuda TY, Fingerhut D, Moreira VC, Camarini PM, Scodeller NF, Duarte A, Jr., Martinelli M, Bryk FF (2013) Open kinetic chain exercises in a restricted range of motion after anterior cruciate ligament reconstruction: a randomized controlled clinical trial. Am J Sports Med 41(4):788–794

19. Granan LP, Forssblad M, Lind M, Engebretsen L (2009) The Scandinavian ACL registries 2004–2007: baseline epidemiology. Acta Orthop 80(5):563–567

20. Hambly K, Griva K (2010) IKDC or KOOS: which one captures symptoms and disabilitie most important to patients who have undergone initial anterior cruciate ligament reconstruction? Am J Sports Med 38(7):1395–1404

21. Hefti F, Muller W, Jakob RP, Staubli HU (1993) Evaluation of knee ligament injuries with the IKDC form. Knee Surg Sports Traumatol Arthrosc 1(3–4):226–234

22. Herbst E, Hoser C, Hildebrandt C, Raschner C, Hepperger C, Pointner H, Fink C (2015) Functional assessments for decision-making regarding return to sports following ACL reconstruction. Part II: clinical application of a new test battery. Knee Surg Sports Traumatol Arthrosc 23(5):1283–1291

23. Higgins LD, Taylor MK, Park D, Ghodadra N, Marchant M, Pietrobon R, Cook C, International Knee Documentation C (2007) Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form. Joint Bone Spine 74(6):594–599

24. Howell SM, Taylor MA (1996) Brace-free rehabilitation, with early return to activity, for knees reconstructed with a double-looped semitendinosus and gracilis graft. J Bone Joint Surg Am 78(6):814–825

25. Howell SM, Hull ML (1998) Aggressive rehabilitation using hamstring tendons: graft construct, tibial tunnel placement, fixation properties, and clinical outcome. Am J Knee Surg 11(2):120–127

26. Howell SM, Knox KE, Farley TE, Taylor MA (1995) Revascularization of a human anterior cruciate ligament graft during the first two years of implantation. Am J Sports Med 23(1):42–49

27. Howell SM, Wallace MP, Hull ML, Deutsch ML (1999) Evaluation of the single-incision arthroscopic technique for anterior cruciate ligament replacement. A study of tibial tunnel placement, intraoperative graft tension, and stability. Am J Sports Med 27(3):284–293

28. Ihara H, Miwa M, Deya K, Torisu K (1996) MRI of anterior cruciate ligament healing. J Comput Assist Tomogr 20(2):317–321

29. Janssen RP, Scheffler SU (2014) Intra-articular remodelling of hamstring tendon grafts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 22(9):2102–2108

30. Janssen RP, Scheffler SU (2014) Remodeling of hamstring tendon grafts after ACL reconstruction. In: Siebold R, Dejour D, Zaffagnini S (eds) Anterior Cruciate Ligament Reconstruction A Practical Surgical Guide. Springer

31. Janssen RP, Scheffler SU (2016) Graft remodeling & ligamentization after ACL reconstruction. In: Prodromos CC (ed) The Anterior Cruciate Ligament. Reconstruction and Basic Science. 2nd edn. Saunders, an imprint of Elsevier, Inc

32. Janssen RP, van der Velden MJ, Pasmans HL, Sala HA (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21(4):898–905

33. Janssen RP, du Mée AW, van Valkenburg J, Sala HA, Tseng CM (2013) Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and ts predictors. Knee Surg Sports Traumatol Arthrosc 21(9):1977–1988

34. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299–1306

35. Kaeding CC, Aros B, Pedroza A, Pifel E, Amendola A, Andrish JT, Dunn WR, Marx RG, McCarty EC, Parker RD, Wright RW, Spindler KP (2011) Allograft versus autograft anterior cruciate ligament reconstruction: predictors of failure from a MOON prospective longitudinal cohort. Sports Health 3(1):73–81

36. Karlsson J, Becker R (2015) Return to sports after ACL reconstruction: individual considerations. Knee Surg Sports Traumatol Arthrosc 23(5):1271–1272

37. Kocher MS, Smith JT, Iversen MD, Brustowicz K, Ogunwole O, Andersen J, Yoo WJ, McFeely ED, Anderson AF, Zurakowski D (2011) Reliability, validity, and responsiveness of a modified International Knee Documentation Committee Subjective Knee Form (Pedi-IKDC) in children with knee disorders. Am J Sports Med 39(5):933–939

38. Kruse LM, Gray B, Wright RW (2012) Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. J Bone Joint Surg Am 94(19):1737–1748

39. Kurosaka M, Yoshiya S, Mizuno T, Mizuno K (1998) Spontaneous healing of a tear of the anterior cruciate ligament. A report of two cases. J Bone Joint Surg Am 80(8):1200–1203

40. Kvist J, Kartus J, Karlsson J, Forssblad M (2014) Results from the Swedish national anterior cruciate ligament register. Arthroscopy 30(7):803–810

41. Macaulay AA, Perfetti DC, Levine WN (2012) Anterior cruciate ligament graft choices. Sports Health 4(1):63–68

42. Macey H (1939) A new operative procedure for repair of ruptured cruciate ligament of the knee. Joint Surg Gynecol Obstet 69:108–109

43. Mall NA, Chalmers PN, Moric M, Tanaka MJ, Cole BJ, Bach BR, Jr., Paletta GA, Jr. (2014) Incidence and trends of anterior cruciate ligament reconstruction in the UnitedStates. Am J Sports Med 42(10):2363–2370

44. Marumo K, Saito M, Yamagishi T, Fujii K (2005) The "ligamentization" process in human anterior cruciate ligament reconstruction with autogenous patellar and hamstring tendons: a biochemical study. Am J Sports Med 33(8):1166–1173

45. McCulloch PC, Lattermann C, Boland AL, Bach BR, Jr. (2007) An illustrated history of anterior cruciate ligament surgery. J Knee Surg 20(2):95–104

46. Menetrey J, Duthon VB, Laumonier T, Fritschy D (2008) "Biological failure" of the anterior cruciate ligament graft. Knee Surg Sports Traumatol Arthrosc 16(3):224–231

47. Middleton KK, Hamilton T, Irrgang JJ, Karlsson J, Harner CD, Fu FH (2014) Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1. Knee Surg Sports Traumatol Arthrosc 22(7):1467–1482

48. Nagda SH, Altobelli GG, Bowdry KA, Brewster CE, Lombardo SJ (2010) Cost analysis of outpatient anterior cruciate ligament reconstruction: autograft versus allograft. Clin Orthop Relat Res 468(5):1418–1422

49. Nordenvall R, Bahmanyar S, Adami J, Stenros C, Wredmark T, Fellander-Tsai L (2012) A population-based nationwide study of cruciate ligament injury in Sweden, 2001-2009: incidence, treatment, and sex differences. Am J Sports Med 40(8):1808–1813

50. Nyland J, Brand E, Fisher B (2010) Update on rehabilitation following ACL reconstruction. Open Access J Sports Med 1:151–166

51. Oiestad BE, Engebretsen L, Storheim K, Risberg MA (2009) Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med 37(7):1434–1443

52. Prodromos C, Joyce B, Shi K (2007) A meta-analysis of stability of autografts compared to allografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 15(7):851–856

53. Renstrom PA (2013) Eight clinical conundrums relating to anterior cruciate ligament (ACL) injury in sport: recent evidence and a personal reflection. Br J Sports Med 47(6):367–372

54. Rosenberg TD, Deffner KT (1997) ACL reconstruction: semitendinosus tendon is the graft of choice. Orthopedics 20(5):396, 398

55. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16(9):834–842

56. Shaarani SR, O'Hare C, Quinn A, Moyna N, Moran R, O'Byrne JM (2013) Effect of prehabilitation on the outcome of anterior cruciate ligament reconstruction. Am J Sports Med 41(9):2117–2127

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

58. Shelbourne KD, Klotz C (2006) What I have learned about the ACL: utilizing a progressive rehabilitation scheme to achieve total knee symmetry after anterior cruciate ligament reconstruction. J Orthop Sci 11(3):318–325

59. Shelbourne KD, Klootwyk TE, Decarlo MS (1992) Update on accelerated rehabilitation after anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 15(6):303–308

60. Shelbourne KD, Vanadurongwan B, Gray T (2007) Primary anterior cruciate ligament reconstruction using contralateral patellar tendon autograft. Clin Sports Med 26(4):549–565

61. Singhal MC, Gardiner JR, Johnson DL (2007) Failure of primary anterior cruciate ligament surgery using anterior tibialis allograft. Arthroscopy 23(5):469–475

62. Stoehr A, Mayr H, Wondrasch B, Fink C (2014) Rehabilitation and return to sports. In: Siebold R, Dejour D, Zaffagnini S (eds) Anterior Cruciate Ligament reconstruction-A Practical Surgical Guide. Springer

63. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res(198):43–49

64. van Grinsven S, van Cingel RE, Holla CJ, van Loon CJ (2010) Evidence-based rehabilitation following anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 18(8):1128–1144

65. Vektis. Personal communication 2015

66. Walden M, Hagglund M, Magnusson H, Ekstrand J (2011) Anterior cruciate ligament injury in elite football: a prospective three-cohort study. Knee Surg Sports Traumatol Arthrosc 19(1):11–19

67. Warner SJ, Smith MV, Wright RW, Matava MJ, Brophy RH (2011) Sport-specific outcomes after anterior cruciate ligament reconstruction. Arthroscopy 27(8): 1129–1134

68. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part I: continuous passive motion, early weight bearing, postoperative bracing, and home-based rehabilitation. J Knee Surg 21(3):217–224

69. Yabroudi MA, Irrgang JJ (2013) Rehabilitation and return to play after anatomic anterior cruciate ligament reconstruction. Clin Sports Med 32(1):165–175

70. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Tsapralis K, Ricci M, Bragonzoni L, Della Villa S, Marcacci M (2014) Return to sport after anterior cruciate ligament reconstruction in professional soccer players. Knee 21(3):731–735

71. Zarins B, Rowe CR (1986) Combined anterior cruciate-ligament reconstruction using semitendinosus tendon and iliotibial tract. J Bone Joint Surg Am 68(2):160–177

ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION AND ACCELERATED BRACE-FREE REHABILITATION: A SYSTEMATIC REVIEW PART I. HAMSTRING TENDON AUTOGRAFT

Rob P.A. Janssen, Nicky Engelen-van Melick, Jan B.A. van Mourik, Max Reijman, Lodewijk W. van Rhijn

European Journal of Physical and Rehabilitation Medicine (under review)

2

Abstract

Background
A major challenge in postoperative rehabilitation after ACL reconstruction is optimizing the balance between muscular strengthening exercises and loading of the graft without compromising graft integrity.

Aim
To summarize the current knowledge on accelerated rehabilitation after hamstring tendon autograft ACL reconstruction.

Design
Systematic review, all settings.

Population
Study designs that reported clinical outcome in adults after arthroscopic, primary ACL reconstruction with accelerated brace-free rehabilitation.

Methods
A search was performed from January 1, 1990 till December 31, 2014 in Medline (Pubmed), EMBASE (OVID), Cochrane Library and CINAHL according to PRISMA guidelines. A risk of bias assessment of the eligible articles was determined. Data collection included surgical techniques, graft type, patient demographics, details of rehabilitation, patient-reported outcome, clinical outcome measures and radiological evaluation. A 'best-evidence synthesis' was performed for the formulated research questions. Fourty-five studies were included in the study. Part I presents the current knowledge on accelerated rehabilitation after hamstring tendon ACL reconstruction.

Results
After hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation: (1) anatomic reconstructions showed better results than nonanatomic reconstructions; (2) there was no difference between single- and double-bundle reconstructions; (3) gender and age did not influence clinical outcome; (4) femoral and tibial tunnel widening occurred; (5) early start of open kinetic exercises at 4 weeks in a limited range of motion (90°-45°) and progressive concentric and eccentric exercises from 12 weeks did not alter outcome; (6) Nintendo Wii® activities could address physical therapy goals; (7) hamstring tendons regenerated after harvest and (8) biological knowledge did not support return to sports at 4-6 months.

Conclusion
Accelerated brace-free rehabilitation may contribute to successful ACL reconstruction with hamstring tendon autografts in adult patients of all ages and gender. Further research is necessary to define the optimal balance of graft loading and graft healing in the various rehabilitation phases after ACL reconstruction as well as the development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual safe return to sports.

Clinical rehabilitation impact
The commonly used accelerated rehabilitation protocol after ACL reconstruction needs to be customized and graft remodelling does not support return to sports at 4-6 months.

Keywords
Hamstring tendon autograft · ACL reconstruction · Accelerated rehabilitation · Clinical outcome · Graft remodelling

Level of evidence III

Introduction

Successful anterior cruciate ligament (ACL) reconstruction requires understanding of several factors: anatomic graft placement, mechanical properties of the selected graft tissue, mechanical behaviour and fixation strength of fixation materials as well as the biological processes that occur during graft remodelling, maturation and incorporation.[45, 59, 90] They influence directly the mechanical properties of the knee joint after ACL reconstruction and, therefore, determine the rehabilitation and time course until normal function of the knee joint can be expected.[49]

The choice of hamstring tendons as graft for ACL reconstruction has increased in popularity.[73] After surgery, graft healing is characterized by a remodelling process.[45, 48, 57, 59] During this period, the graft will undergo changes, becoming morphologically similar to intact ligament tissue.[33, 45, 48, 75]

Advantages of accelerated brace-free rehabilitation after ACL reconstruction are earlier normal function of the knee, weight-bearing and ability to return to even most strenuous activities after primary ACL reconstruction at 6 months.[4, 14, 33, 43, 45, 56, 81, 91, 98]
A major challenge in postoperative rehabilitation after ACL reconstruction is optimizing the balance between muscular strengthening exercises and loading of the graft, to stimulate graft cells to produce cellular and extracellular components for preservation of graft stability, without compromising graft integrity, which might result into an early stretch-out of the ACL reconstruction.[14, 45, 53, 75, 94]

The primary aim of this systematic review is to investigate the clinical outcome of accelerated brace-free rehabilitation after ACL reconstruction in adults. The secondary aims are the influence of accelerated rehabilitation after ACL reconstruction on tunnel widening, tendon regeneration and time to return to sports. The systematic review is presented in two parts in order to give a better overview of the results of different graft types for ACL reconstruction. This first part will present the current knowledge on accelerated rehabilitation after hamstring tendon autograft ACL reconstruction.

Materials and methods

A systematic literature search was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines using a PRISMA checklist.[55]

Eligibility criteria
Inclusion criteria were all study designs reporting outcome after ACL reconstruction with brace-free accelerated rehabilitation. Only studies on human adults with isolated ACL ruptures were eligible for inclusion in the systematic review. Studies on children, adolescents with open physis and cadavers were not included. Hamstring and patellar tendon autografts for ACL reconstruction were included. Therapeutic studies comparing accelerated rehabilitation with nonaccelerated rehabilitation, no reconstruction, wait-and-see, brace or no comparison at all were included. Outcome was defined as subjective (questionnaires), objective (strength, hop-indices), knee stability (passive and active), functional performance, level of activity, return to sports and osteoarthritis. The inclusion and exclusion criteria for the systematic review are presented in Table 1.

Electronic search
A systematic electronic search was performed using specific search terms in the following databases: Medline (Pubmed), EMBASE (OVID), the Cochrane Library and CINAHL. The time range for the search was defined as January 1, 1990 till December 31, 2014.

Study selection
All eligible articles were screened by title and abstract by 2 teams of reviewers (RJ&NE and RJ&JM). When two reviewers did not reach consensus, a third reviewer (NE or JM) made the final decision. After this first inclusion, the full-text articles were assessed. These were excluded if they did not meet the inclusion criteria. Furthermore, all references of both excluded and included articles were analysed for eligible articles.

Data collection process
Two reviewers (RJ&NE) independently extracted the data from each study. Disagreement regarding data extraction was resolved by consensus.

Data items
The data included surgical techniques, graft type, patient demographics, details of rehabilitation, patient-reported outcome, clinical outcome measures and radiological evaluation.

Synthesis of results
Due to substantial heterogeneity with regard to surgical techniques, populations, outcome and study designs, it was not possible to pool the data for statistical analysis. Therefore, a 'best-evidence synthesis'[83] was performed, by means of the system developed by van Tulder et al.[92] The following ranking of levels of evidence was formulated:

1. Strong evidence is provided by 2 or more studies with good quality (low risk of bias) and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings).
2. Moderate evidence is provided by 1 good quality (low-risk of bias) study and 2 or more questionable quality (higher risk of bias) studies and by generally consistent findings in all studies (≥ 75%).
3. Limited evidence is provided by 1 or more questionable quality (higher risk of bias) studies or 1 good quality (low-risk of bias) study and by generally consistent findings (≥ 75%).
4. Conflicting evidence is provided by conflicting findings (< 75% of the studies reported consistent findings).[92]

Assessment of risk of bias
Two reviewers (RJ&NE) assessed the risk of bias of the articles. If the 2 reviewers did not reach consensus, a third reviewer (JM) made the final decision. The reviewers were not blinded for author, journal or publication. The assessment of risk of bias of all articles was performed by standardized checklists of the Cochrane Library (www.cochrane.nl).

The assessment of risk of bias for randomized controlled trials (RCT) used 9 criteria, displayed in Table 2. These 9 items could be rated 'yes' (+), 'no' (-) or 'do not know' (?). The same list was used for assessing clinical controlled trials (CCT), but these scored a 'no' for items 1 and 2.

The assessment of risk of bias for cohort studies described 8 items, displayed in Table 2. All 8 items could be rated 'positive' (+), 'negative' (-) or 'do not know' (?). The same list was used for cross-sectional studies, but these scored a 'no' for item 2 because the study design could cause a selection bias.

Based on the research question, 2 additional items were evaluated: (1) accurate description of the rehabilitation protocol and (2) ratio of men and women participating in the study.
A total score was calculated by adding up all positive items. A final judgment of 'good', 'questionable' or 'poor' was given to every article. A 'good' was assigned to articles scoring positive for more than 50% of all items (low risk of bias); a 'questionable' if the positive score was between 30-50% (questionable risk of bias) and a 'poor' was assigned to articles with a positive score inferior to 30% (high risk of bias). The articles with a total score of 'good' and 'questionable' were included in the review.

Research questions
The following research questions were formulated:

1. How do different nonanatomic and anatomic surgical techniques affect the clinical outcome after accelerated brace-free rehabilitation?
2. How do different patient characteristics affect the clinical outcome after accelerated brace-free rehabilitation?
3. Does accelerated brace-free rehabilitation after ACL reconstruction influence tunnel widening?
4. How do differences in rehabilitation protocols affect the clinical outcome after accelerated brace-free rehabilitation?
5. Do hamstring tendons regenerate after harvest for ACL reconstruction with accelerated brace-free rehabilitation?
6. Does the current biological knowledge on hamstring autografts support early return to sports after ACL reconstruction with accelerated brace-free rehabilitation?

Results

Study selection
The PRISMA flow chart of the systematic review is presented in Fig. 1. A total of 52 studies were selected for risk of bias assessment: 20 randomized controlled trials (RCT),[8, 11, 20, 29, 32-36, 39, 40, 51, 54, 61, 62, 69, 74, 76, 77, 89] 12 clinical controlled trials (CCT),[23, 24, 52, 58, 66, 67, 71, 72, 79, 85, 87, 96] 9 prospective cohort studies (PC),[15, 17, 25, 28, 42-44, 46, 100] 7 cross-sectional studies (CS),[3, 18, 19, 22, 26, 48, 84] 3 retrospective cohort studies (RC)[2, 50, 88] and 1 case study.[27]

Risk of bias assessment
The results of the risk of bias assessment for the included studies are presented in Tables 3 and 4. Seven articles were discarded because of the total score 'poor' after quality appraisal. Forty-five articles were included in the systematic review.

Details of rehabilitation
The results of the specific details of accelerated rehabilitation of the 45 included studies are presented in Table 5.

Results of individual studies and answers to research questions

1. *How do different nonanatomic and anatomic surgical techniques affect the clinical outcome after accelerated brace-free rehabilitation?*

a. Four-strand hamstring single-tunnel (nonanatomic) ACL reconstruction
Howell et al.[43] were among the first authors to present the clinical outcome of accelerated brace-free rehabilitation.[43] This single-surgeon prospective cohort series described a 4-strand hamstring transtibial ACL reconstruction technique with special attention to intercondylar roof impingement of the graft. Patients returned to unrestricted sports and work activities after 4 months. At 4 months, 33 (82%) of the 37 patients had an absent pivot shift and a normal Lachman test. The authors justified the early return to vigorous activities at 4 months by unchanged knee stability, girth of the thigh, knee extension as well as Lysholm and Gillquist scores at 2-year follow-up. The one-leg hop for distance test still improved between 4 months and 2 years. Final IKDC (International Knee Documentation Committee) score at 2 years was rated A in 63%, B in 27%, and C in 10% of patients.[43]

Ali et al.[3] presented the outcome of a single-surgeon, cross-sectional study of transtibial nonanatomic ACL reconstructions using a 4-strand hamstring graft without detachment of its tibial insertion. Follow-up was 64 months (range 48- 84). All patients achieved full range of motion with a stable joint. The mean side- to-side difference using KT-1000 was 1.43 (SD 3.86, MEDmetric Co., San Diego, CA, USA). At the latest follow-up, all patients had a negative pivot shift test. The average Lysholm score improved from 42 to 79.2 and the Tegner score improved from 3.4 to 5.9 (the preinjury score was 6.9). The authors concluded that their technique showed satisfactory and comparable results to studies with conventional detachment of hamstring tendons from their tibial insertion.[3]

Zaffagnini et al.[100] analysed return to sports in a homogeneous group of male professional football (soccer) players after ACL reconstruction. Follow-up was 4 years. The authors used a nonanatomic, 4-strand hamstring technique with additional extra-articular fixation of the graft. After 12 months, 20 (95%) of the 21 patients returned to the preoperative professional football level. Mean time from surgery to first official match was 186 days (range 107-282). The KOOS (Knee injury and Osteoarthritis Outcome Score) reached the plateau level at 6 months postoperatively. At 4 years, 15 patients (71%) still played professional football, 13 (62%) at the same preoperative level and 2 (9%) in a lower division. One patient (5%) experienced a rerupture of the ACL reconstruction.[100]

Nonanatomic transtibial 4-strand hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation is associated with good clinical results. Return to sports is possible at 4-6 months postsurgery ('strong' level of evidence).

b. Nonanatomic versus anatomic hamstring tendon ACL reconstruction
Koutras et al.[52] compared the short-term functional and clinical outcome between nonanatomic transtibial versus anatomic anteromedial ACL technique in patients with hamstring tendon ACL reconstruction. The outcome measures consisted of Rolimeter laxity testing, Lysholm score, isokinetic and functional testing (single- and triple-hop test, side step, carioca test for time). All outcomes, except isokinetic knee flexion at 180°/s, improved from 3 to 6 months for both groups. The anteromedial approach group had better Lysholm scores at 3 months and better performance in the timed lateral movement functional tests at 3 and 6 months. All other comparisons were nonsignificant.[52]

Anatomic ACL reconstruction shows better short-term results than nonanatomic ACL reconstruction after accelerated brace-free rehabilitation ('moderate' level of evidence).

c. Single-bundle versus double-bundle hamstring tendon ACL reconstruction
Sastre et al.[74] compared anatomic 4-strand single- and double-bundle hamstring tendon ACL reconstructions in a randomized prospective study. The authors did not find any difference between the two groups with respect to anterior laxity (manual and radiological), pivot shift test as well as IKDC subjective and objective scores.[74]

Czamara et al.[25] analysed single- versus double-bundle ACL reconstructions with focus on knee function assessment during activities involving dynamic knee rotation. No differences were noted between the 2 groups for anterior tibial translation, pivot shift test, range of motion, joint circumference, subjective assessment of pain and knee joint stability, peak torque for internal and external rotation and the run test with maximal speed and change of direction manoeuvres.[25]

There is no difference in clinical results between single-bundle and double-bundle ACL reconstruction with accelerated brace-free rehabilitation ('strong' level of evidence).

2. *How do different patient characteristics affect the clinical outcome after accelerated brace-free rehabilitation?*

a. Gender
Salmon et al.[72] investigated gender differences in outcome after ACL reconstruction in a single-surgeon series. The reconstruction performed was a 4-strand hamstring, anteromedial femoral tunnel drilling technique with interference screw fixation. Outcome measures were the IKDC score, KT- 1000 arthrometer, Lysholm score and level of sports activity. Follow-up was at 12, 24 and 84 months after surgery. No significant gender differences were found for graft rupture, activity level, self-reported or functional assessment or radiological outcome. Women did have significantly greater laxity than men on the Lachman test, pivot shift test and mean manual maximum testing at all time points. The higher laxity measurements did not influence the self-reported and functional outcome assessments.[72]

Gender does not influence clinical outcome after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation ('limited' level of evidence).

b. Age
Trojani et al.[88] retrospectively analysed the same ACL reconstruction technique as Salmon et al.[72] in 18 patients aged 50 years and older. None of the patients experienced subjective instability or had complaints on kneeling. Pain was associated with previous medial meniscectomy. Graft failure did not occur. At follow-up (median 31 months), overall IKDC was A in 7 patients (39%), B in 7 (39%), C in 3 (17%) and D in 1 patient (5%). The authors concluded that age over 50 years is not a contraindication to select a hamstring tendon autograft for ACL reconstruction. Surgery restored knee stability but did not modify pain in patients with previous medial meniscectomy.[88]

Age > 50 years does not influence clinical outcome after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation ('limited' level of evidence).

3. *Does accelerated brace-free rehabilitation after ACL reconstruction Influence tunnel widening?*

Vadalà et al.[89] analysed tunnel widening after 4-strand hamstring tendon ACL reconstruction by means of CT scan comparing accelerated brace-free rehabilitation versus nonaccelerated rehabilitation with brace. Mean follow-up was 10 months. There was a significant increase in femoral and tibial tunnel diameter after accelerated brace-free rehabilitation.[89]

Accelerated brace-free rehabilitation after hamstring tendon ACL reconstruction causes increased tunnel widening in both femur and tibia ('moderate' level of evidence).

4. *How do differences in rehabilitation protocols affect the clinical outcome after accelerated brace-free rehabilitation?*

The effects of early aggressive versus nonaggressive rehabilitation were examined by Christensen et al.[20] In a single-surgeon anatomic 4-strand hamstring tendon ACL reconstruction series, the primary outcome measure was the IKDC score. Secondary outcome measures were differences in range of motion and peak isometric force at 12 weeks postsurgery. No differences were found between early aggressive and nonaggressive rehabilitation for both primary and secondary outcome measures.[20]

Fukuda et al.[33] evaluated the outcome of early start of open kinetic chain exercises in a restricted range of motion at 1 year after nonanatomic, 4-strand hamstring tendon ACL reconstruction. Outcome measures were pain, muscle strength, anterior knee laxity (Rolimeter) and function (single-leg hop test, cross-over test, Lysholm score). A start of open kinetic chain quadriceps exercises at 4 weeks postoperatively in a restricted range of motion (90°-45°) did not differ from a start at 12 weeks in terms of anterior knee laxity, pain and functional improvement. The early start group showed a faster recovery of quadriceps strength.[33]

The effect of progressive eccentric and concentric training on functional performance after 4-strand hamstring tendon ACL reconstruction was investigated by Kinikli et al.[51] Outcome measures were isokinetic muscle strength, single- and vertical hop tests, Lysholm score and ACL-Quality of Life Questionnaire. There was a significant improvement of all outcome measures except for isokinetic strength of knee extensors and flexors.[51]

Baltaci et al.[8] compared a 12-week Nintendo Wii® Fit versus conventional accelerated brace-free rehabilitation after hamstring tendon ACL reconstruction. Outcome measures were coordination, proprioception, response time, dynamic balance and isokinetic tests. The two different 12-week physiotherapy protocols had the same effect on muscle strength, dynamic balance and functional performance values.[8]

Clark et al.[22] used the Nintendo Wii® Fit Balance Board to assess weight-bearing asymmetry during squatting after hamstring tendon ACL reconstruction. The authors found significant increases in asymmetry after ACL reconstruction compared to a matched control group.[22]

Early aggressive rehabilitation after hamstring tendon ACL reconstruction, early start of open kinetic chain quadriceps exercises at 4 weeks in a limited knee range of motion (90°- 45°) and progressive concentric and eccentric exercises from 12 weeks does not alter the clinical outcome ('moderate' level of evidence). The use of Nintendo Wii® Fit activities could address physical therapy goals ('limited level' of evidence).

5. *Do hamstring tendons regenerate after harvest for ACL reconstruction with accelerated brace-free rehabilitation?*
Ahlen et al.[2] analysed regeneration of hamstring tendons in a retrospective MRI study with 6-year follow-up after hamstring tendon harvest. The gracilis tendon regenerated in 18 of 19 patients, the semitendinosus tendon in 17 of 19 patients.[2]

Janssen et al.[46] performed a prospective MRI study in 22 patients with follow-up at 6 and 12 months. Regeneration of the gracilis tendon occurred in all patients, the semitendinosus tendon regenerated in 14 of 22 patients. The majority of tendons regenerated distal to the joint line of the knee. The authors did not find a significant relationship between tendon regeneration and isokinetic flexion strength.[46]

Hamstring tendons regenerate after harvest for ACL reconstruction. There is no evidence to support a relationship between tendon regeneration and increased isokinetic flexion strength ('strong' level of evidence).

6. *Does the current biological knowledge on hamstring autografts support early return to sports after ACL reconstruction with accelerated brace-free rehabilitation?*

Janssen et al.[48] examined 67 patients who underwent retrieval of mid-substance biopsies after clinically successful 4-strand hamstring autograft ACL reconstruction with a standardized accelerated rehabilitation protocol. Histology, cellular density, vascular density, myofibroblast density and collagen fibril alignment were analysed. Cellular density and vascular density were increased up to 24 months after ACL reconstruction. Especially the strong increase in myofibroblast density, from 13 up to 24 months, indicated an active remodelling process from 1 to 2 years. Furthermore, vessel density increased over 24 months, whereas cell and myofibroblast density decreased but stayed higher than native hamstring tendon and ACL controls. Collagen orientation did not return to normal in the study period. The authors question whether early return to sports (4-6 months) after accelerated rehabilitation is to be recommended after hamstring tendon ACL reconstruction.[48]

Intra-articular hamstring graft remodelling is still active at 2 years after ACL reconstruction with an accelerated brace-free rehabilitation. Based on the current evidence, the early return to sports after 4-6 months may be questionable ('moderate' level of evidence).

Discussion

A significant body of literature has shown that accelerated rehabilitation, defined as early unrestricted motion, immediate weight-bearing, and eliminating the use of immobilizing braces, is appropriate after ACL reconstruction with patellar tendon grafts.[14, 16, 19, 20, 26, 70, 78, 80, 82] However, conclusions are unclear when evaluating the effects of early accelerated rehabilitation after ACL reconstruction with hamstring autografts.

There are several factors that need to be considered when accelerated brace-free rehabilitation after ACL reconstruction with hamstring tendons is prescribed.[31]
First, hamstring autografts require fixation of soft tissue (tendon) to bone.[63] A period of 8 to 12 weeks is necessary for proper incorporation of hamstring grafts in the bone tunnels.[31] Fixation of this soft tissue graft is considered the 'weak link' early on after ACL reconstruction.[31, 37] Secure graft fixation during progressively more intense early rehabilitation and activities of daily living improves graft-bone tunnel integration.[37] In a systematic review of 14 papers, Han et al. concluded that both intratunnel and extratunnel fixation methods of hamstring tendon ACL autografts displayed comparable outcomes based on objective IKDC-, Lysholm- and Tegner scores, anterior knee laxity and return to sports timing.[37]

Second, the intra-articular remodelling of ACL hamstring tendon autografts requires an optimal balance between muscular strengthening exercises and loading of the graft. This will stimulate ACL graft cells to produce cellular and extracellular components for preservation of graft stability, without compromising graft integrity, which might result into an early stretch-out of the ACL reconstruction.[12, 14, 45, 75, 94]

Finally, early after ACL reconstruction, relative protection of the autograft donor site must be considered. Therefore, force generation from the hamstrings should be minimized when a hamstring autograft is employed.[31]
In summary accelerated brace-free rehabilitation needs to be as aggressive as possible in restoring function while still maintaining an optimal tissue healing environment.[64]

This review presented a 'moderate' level of evidence that early aggressive rehabilitation after hamstring tendon ACL reconstruction did not alter clinical outcome compared to nonaggressive rehabilitation.[20] In this study, nonaggressive therapy included partial weight-bearing and 4-week use of an immobilizer brace. In contrast, the aggressive rehabilitation was brace-free, with immediate weight-bearing allowed.[20]

The rationale of using a knee brace is to protect the healing graft during the early phases of rehabilitation.[4] Various systematic reviews could not substantiate this hypothesis based on clinical results.[4, 53, 91, 97] Functional knee bracing may even have negative consequences. In a 3D lower-extremity-kinematic and electromyography study of treadmill running with or without functional knee brace use, the braced knees showed a decreased range of motion, increased hamstring activation and decreased quadriceps femoris activation.[64]

The latest review by Kruse et al. concluded that bracing following ACL reconstruction is neither necessary nor beneficial and adds to the costs of the procedure.[53] Furthermore, full weight-bearing without crutches within 10 days (with a normal gait pattern) improves quadriceps function, prevents patellofemoral pain and does not affect knee stability.[91, 97]

This review showed that early start of open kinetic chain quadriceps exercises at 4 weeks in a limited knee range of motion (90°-45°) did not alter the clinical outcome after hamstring tendon ACL reconstruction ('moderate' level of evidence).[33] Open kinetic chain or non weight-bearing exercises can provide superior isolated muscle or muscle group recruitment and ease of strength measurement. Closed kinetic chain or weight-bearing exercises can provide superior integrated lower extremity neuromuscular recruitment and ease of composite strength or power measurement. The prescriptive use of both open and closed kinetic chain exercises enables patients to develop the dynamic lower extremity stability and neuromuscular control needed to protect the healing graft.[64]

Beynnon et al.[13] found similar maximum native ACL strain values produced by squatting (a closed kinetic chain exercise) and active flexion-extension (an open kinetic chain exercise). They also demonstrated that increasing resistance during the squat exercise did not produce a significant increase in native ACL strain values, unlike increased resistance during active flexion-extension exercise.[13]

Escamilla et al.[31] published a biomechanical review on native ACL strain and tensile forces in open kinetic and closed kinetic exercises. Open kinetic exercises generally loaded the ACL more than closed kinetic exercises and that, for both exercises, the ACL was loaded to a greater extent between 10° and 50° compared to 50° and 100° of knee flexion.[31] These biomechanical findings are in agreement with the good clinical results with the start of open kinetic exercises at 4 weeks in a limited range of motion as presented in this review.[33, 47, 48]

Van Grinsven et al. concluded in their systematic review on evidence-based rehabilitation after ACL reconstruction that there is increasing consensus that open kinetic chain exercises do not increase graft laxity (in and exceeding the safe range with a focus on endurance). Additionally, these exercises had a favourable effect on quadriceps strength.[91]

Majima et al.[56] also demonstrated that accelerated rehabilitation with start of open kinetic exercises at 7-10 days after hamstring tendon ACL reconstructions could rapidly restore muscle strength without significantly compromising graft stability. However, the incidence of synovitis of the knee was significantly increased after accelerated rehabilitation.[56]

This review has shown that progressive concentric and eccentric exercises from 12 weeks after surgery did not alter the clinical outcome after hamstring tendon ACL reconstruction ('moderate' level of evidence).[51] Therapeutic exercises that emphasize eccentric gluteus maximus, quadriceps femoris and gastrocnemius-soleus activation can improve lower extremity muscular shock absorption, prevent knee reinjury, enhance athletic performance, help heal lower extremity musculotendinous injuries, increase bone mineral density and decrease fall risk.[64]

Kruse et al. concluded that starting eccentric quadriceps strengthening and isokinetic hamstring strengthening 3 weeks after ACL surgery may improve or accelerate strength gains.[53] The studies in their systematic review compared hamstring and patellar tendon autografts.[53]

Specific investigation of accelerated strengthening rehabilitation protocols and their ability to shorten the return to sport time frame after hamstring tendon ACL reconstruction is warranted. Further research is necessary to determine the optimal timing of introducing open kinetic exercises and safe amount of progressive resistance training after hamstring tendon ACL reconstruction.[1, 91]

A critical remark is necessary when accelerated rehabilitation is discussed. There is little consensus in the literature about what composes an accelerated rehabilitation protocol because few papers have described their protocol adequately.[91] In this review, almost all included studies on accelerated brace-free rehabilitation agreed that immediate weight-bearing, full range of motion and closed kinetic exercises were permitted after hamstring tendon ACL reconstruction. However, if even specified at all, the protocols varied in their timing and details of open kinetic chain exercises, frequency of concentric and eccentric training as well as neuromuscular training.

Many studies on accelerated rehabilitation after hamstring tendon ACL reconstruction reported the use of the accelerated rehabilitation protocols designed and validated only for patellar tendon autograft ACL reconstructions.[16, 70, 78, 82] Only four of the studies described a specific protocol for accelerated rehabilitation after hamstring tendon ACL reconstruction.[43, 46, 48, 95] Wilk et al.[95] recommended the avoidance of early aggressive hamstring resistive exercises in the first 6 weeks. Other rehabilitation differences between patellar tendon and hamstring grafts included no running for 10-12 weeks, no jumping for 12-14 weeks, no twisting or hard cutting for 16 weeks, and a return to sports at 4-6 months.[46, 48, 95]

The rehabilitation protocol by Shelbourne&Nitz was most often cited. This protocol emphasized specific presurgical rehabilitation goals.[23, 24, 26, 46, 61-63] Remarkably, only 4 studies in this review specified their prehabilitation.[46, 48, 52, 84] Furthermore, although referring to the aforementioned rehabilitation protocol, the timing of return to activities such as running or unrestricted sports varied widely among studies, often without specific criteria.

The lack of details of accelerated rehabilitation protocols after hamstring tendon ACL reconstructions makes it difficult to evaluate the potential disadvantages of accelerated rehabilitation such as tunnel widening[23, 89] and increased synovitis.[56] Postoperative rehabilitation is a major factor contributing to the success of ACL reconstruction and needs to be defined in detail for adequate research on clinical outcome and safe return to sports.

Based upon anecdotal success, ACL rehabilitation protocols slowly evolved from a 12 months time frame for return to sports to a generally accepted 6 months time.[98] In the present systematic review, a return to unrestricted sport activities was reported allowed at 4-6 months after accelerated brace-free rehabilitation. In this level IV case series, the authors justified the early return to vigorous activities at 4 months by unchanged knee stability, girth of the thigh, knee extension as well as Lysholm- and Gillquist scores at 2-year follow-up.[43]

In a meta-analysis of 69 articles, Ardern et al.[7] have shown that after ACL reconstruction, the overall return to some kind of sports activity is 81%. Sixty-five per cent of patients returned to their preinjury level and 55% to competitive sports at final follow-up. Younger age, male gender and a positive psychological response all favoured returning to the preinjury level sport. Elite athletes had more than twice the odds of returning to competitive sports compared to nonelite athletes.[7]

Zaffagini et al. have shown a return to preoperative professional football level in 95% of elite male athletes after 1 year with an accelerated brace-free rehabilitation.[100] In another study on professional football, elite male UEFA-league players needed 7 months to return to the first training after ACL reconstruction, 10 months to return to regular practice and 12 months to return to match play.[68, 93]

Leading ACL experts generally let their patients return to play after an average of 6 months, with return to full competition after an average of 8 months.[60] However, a recent study by Herbst et al.[41] showed that most patients, in terms of neuromuscular abilities and compared to healthy controls, were most likely not ready for a safe return to sports, even at 8 months postoperatively. The most limiting factor was a poor limb symmetry index (LSI) value of < 90% if the dominant leg was involved and < 80% if the nondominant leg was involved.[41] Further studies identifying sport-specific differences in ACL reconstruction outcomes in athletes could further enhance accelerated rehabilitation protocols for athletes after ACL reconstruction.[100]

Return to sports is often used as short- to mid-term outcome measure for ACL reconstruction and rehabilitation. However, Harris et al.[38] reported in a systematic review, that 65% of studies did not report whether criteria were used to allow a patient to return to sports. Twenty-four percent of studies did not report when patients were allowed to return to sports without restrictions. Only 10% of studies reported whether patients were able to return at their preinjury level.[38]

Kruse et al. concluded in their review that very few studies actually measured the ability to return to sports and its timing after ACL reconstruction with rehabilitation.[53] In a systematic review on return to sports after ACL reconstructions, only 13% of studies had noted objective criteria required for return to sports.[10] The authors concluded that there is a major lack of objective assessment before release to unrestricted sports activities in the literature. Furthermore, commonly used muscle functional tests are not demanding or sensitive enough to identify differences between injured and noninjured sides.[9, 68]

An interesting factor in return to sports is the expectation of the patient. Although scores may be high on validated clinical measures, the ability to return to sports and performance on return to sports may not meet up to the patient's expectations, thus making the surgery unsuccessful from the patient's perspective. This had been demonstrated in a meta-analysis of nearly 6000 patients after ACL reconstruction.[5] The study showed that only 44% of patients were able to return to competitive sport, despite 90% of patients having normal or nearly normal knee function using validated outcome scores.[6, 38]

Despite the large number of peer-reviewed publications, no conclusive guidelines exist to permit safe return to unrestricted activity.[38, 99] In this systematic review, only 35% of studies reported assessment criteria for return to sports after hamstring tendon ACL reconstruction. These criteria however lacked specific details for use in clinical practice or comparative scientific research.
The development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual return to sports is greatly needed and offers opportunities for further research.[7, 10, 30, 64, 68]

ACL reconstruction techniques have improved over the last 10 years, but graft failure is not uncommon: 0.7-10%.[45, 59] Evidence-based evaluations did not prove a 3-6 months return to sports to be safe due to the fact that biological healing is not complete.[21, 45, 48, 65, 68] This is also demonstrated in the current review: intra-articular hamstring graft remodelling was still active at 2 years after ACL reconstruction with an accelerated brace-free rehabilitation ('moderate' level of evidence).[48] Three systematic reviews on remodelling have been published and described similar stages of ACL graft healing as well as a prolonged remodelling process in humans compared with results obtained from animal studies.[21, 45, 65] While today's rehabilitation protocols are often extrapolated from findings of animal in vivo studies, current findings in human in vivo remodelling studies might require new postoperative regimens following hamstring tendon ACL reconstruction.[45]

Accelerating angiogenesis of the healing graft could promote faster healing. In a systematic review, Tohyama et al.[86] have examined the in vitro effects of vascular endothelial growth factor (VEGF) on hamstring ACL grafts in animals. VEGF treatment promoted a remarkable increase in synovial tissue with hypervascularity around the graft 12 weeks after ACL reconstruction and stimulated angiogenesis and cellular infiltration in the graft. However, biomechanical properties of the graft deteriorated due to soft tissue flaws and digestion of graft matrix by the VEGF treatment. The authors recommended indirect enhancement of VEGF using physical stimulation as strategy to accelerate remodelling without weakening the ACL graft.[86]

It is agreed that ACL graft healing can only progress if mechanical loading occurs: however, the most adequate magnitude at varying phases of healing is still not clarified.[45] No final conclusions can be drawn on the mechanical strength of the healing ACL grafts in humans without any available technique for in vivo measurements of their mechanical properties.[21, 45]

This systematic review has several limitations.
In the search for the available knowledge on clinical outcome after accelerated brace-free rehabilitation after ACL reconstruction, studies of various level of evidence were included. It must be noticed that the type of rehabilitation was not a primary outcome in all of the included studies. Some conclusions of the 'best-evidence synthesis' may therefore not be primarily related to accelerated rehabilitation.

A second limitation of this review is the inclusion of studies with small population size. Both the quality and limited amount of studies for specific research questions may limit the level of evidence in the chosen 'best-evidence synthesis' by van Tulder et al.[92] Although strict and adapted for various study types, the risk of bias assessment of the Cochrane Library and the classifications of 'low', 'questionable' and 'high' risk of bias for the studies may limit the strength of evidence. One might argue that a 'low' risk of bias RCT study might show a higher level of evidence than a 'low' risk of bias prospective cohort study.

Another limitation of this study is that only articles in English were included. Additional relevant articles published in languages other than English could contribute to the level of evidence presented in this review.

Finally, only publications from 1990 onwards were included. Focus of the review was on accelerated rehabilitation, which became more widespread in those years. We might have missed a few earlier publications although all references were checked of all included studies for previous studies.

Conclusion

Accelerated brace-free rehabilitation may contribute to successful ACL reconstruction with hamstring tendons in adult patients of all ages and gender. Further research is necessary to define the optimal balance of graft loading and graft healing in the various rehabilitation phases after ACL reconstruction as well as the development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual safe return to sports.

Figure 1 PRISMA flow chart

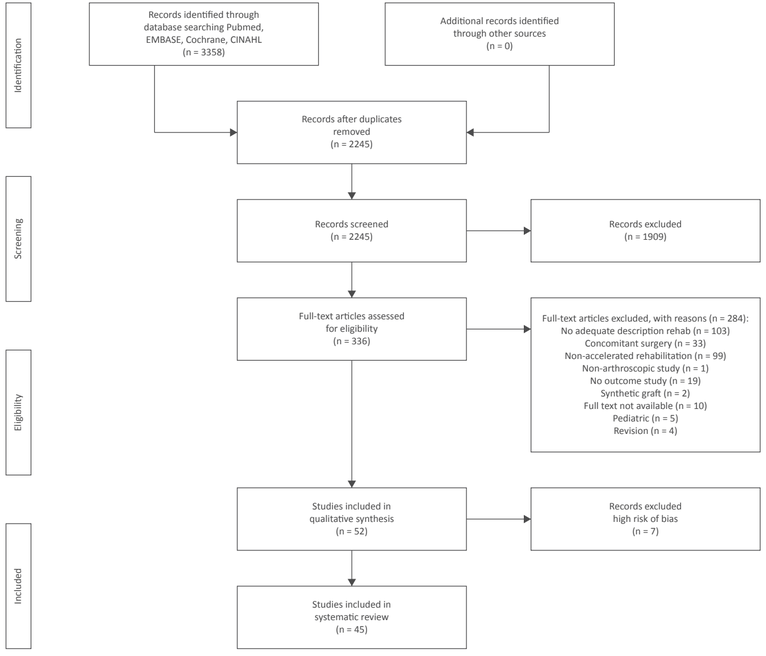


Table 1 Inclusion and exclusion criteria

Inclusion criteria

1) Studies (meta-analysis, randomized, nonrandomized, systematic reviews, case series, prospective or retrospective design) evaluating outcome in patients undergoing isolated ACL reconstruction
2) Studies must have included an accelerated rehabilitation protocol. Accelerated rehabilitation is characterized by immediate postoperative weight-bearing, without restriction in motion and brace-free rehabilitation. Return to sports is allowed after 4-6 months
3) Any arthroscopic surgical method of primary intra-articular ACL reconstruction
4) Hamstring and bone-patellar-tendon bone autograft
5) Human in vivo studies with reported outcome
6) English language
7) Abstract and full text available

Exclusion criteria

1) Concomitant surgery limiting an accelerated rehabilitation protocol (meniscal repair or transplant, osteotomy, microfracture, autologous cartilage implantation -ACI or matrix autologous chondrocyte implantation-MACI)
2) Revision surgery
3) Allografts, quadriceps tendon or synthetic grafts
4) Multiligament reconstructions
5) Posterolateral, medial or posterior cruciate ligament instability
6) Nondefined rehabilitation protocol
7) Animal or cadaveric (in vitro) studies
8) Non-arthroscopic ACL reconstruction
9) Non-English language
10) Abstract or full-text not available

Table 2 Cochrane criteria for assessment of randomized controlled trials and cohort studies

Randomized controlled trials	Cohort studies
1) Is a method of randomization applied?	1) Are study groups clearly defined?
2) Is randomization blinded?	2) Is there any selection bias?
3) Are the patients blinded?	3) Is the exposure clearly defined?
4) Is the therapist blinded?	4) Is the outcome clearly defined?
5) Is the outcome assessor blinded?	5) Is the outcome assessment blinded?
6) Are the groups comparable?	6) Is the follow-up accurate?
7) Is there an acceptable lost-to-follow-up?	7) Is there an acceptable loss-to-follow-up?
8) Is there an intention-to-treat?	8) Are confounders described and/or eliminated?
9) Are treatments comparable?	

Table 3 Risk of bias assessment of RCTs and CCTs

Article	Study design	1	2	3	4	5	6	7	8	9	Accurate description rehabilitation	Ratio men - women	Total score
Baltaci et al.	RCT	+	+	-	?	-	+	+	+	+	+	+	Good
Beard et al.	RCT	+	+	-	?	?	+	-	+	+	+	?	Good
Christensen et al.	RCT	+	+	?	-	-	-	+	+	+	+	+	Good
Clatworthy et al.	CCT	-	-	?	-	?	+	+	?	+	-	+	Questionable
Corry et al.	CCT	-	-	?	-	?	+	+	?	+	+	+	Questionable
Ejerhed et al.	RCT	+	+	?	-	?	+	+	?	+	+	-	Good
Feller et al.	RCT	+	+	?	-	?	+	+	-	+	+	-	Good
Fukuda et al.	RCT	+	+	?	?	+	+	-	+	+	+	-	Good
Gerber et al. 2007	RCT	+	-	?	-	+	?	+	+	+	+	?	Good
Gerber et al. 2009	RCT	+	-	?	-	+	?	+	+	+	+	?	Good
Grant et al.	RCT	+	?	-	?	+	+	-	-	+	+	?	Questionable
Heijne et al. (2007)	RCT	+	+	?	-	-	+	-	?	+	+	+	Good
Heijne et al. (2010)	RCT	+	+	?	-	+	?	?	+	+	+	+	Good
Kinikli et al.	RCT	+	?	+	-	-	+	?	?	+	+	-	Questionable
Koutras et al.	CCT	-	-	+	+	+	+	+	-	+	+	-	Good
Laoruengthana et al.	RCT	+	+	?	-	?	+	+	?	+	+	-	Good
Melikoglu et al.	CCT	-	-	?	?	?	+	?	?	+	+	-	Poor
Mikkelsen et al.	RCT	+	?	?	?	?	+	+	+	+	+	-	Good
Mohammadi et al.	RCT	+	+	-	?	?	+	+	+	+	-	+	Good
Pinczewski et al. (2002)	CCT	-	-	?	-	?	+	+	-	+	+	+	Questionable
Pinczewski et al. (2007)	CCT	-	-	?	-	?	+	+	-	+	+	+	Questionable
Revenas et al.	RCT	+	?	?	-	+	+	-	?	+	+	-	Questionable
Rudroff et al.	CCT	-	-	-	?	?	+	+	+	+	+	-	Questionable
Salmon et al.	CCT	-	-	?	?	?	?	-	?	+	+	+	Questionable
Sastre et al.	RCT	+	+	?	?	?	+	+	+	+	+	+	Good
Schenck et al.	RCT	+	+	?	-	?	?	?	+	+	+	-	Questionable
Shaarani et al.	RCT	+	+	-	?	?	+	?	-	+	-	+	Questionable
Shelbourne et al.	CCT	-	-	?	?	?	+	-	?	+	+	-	Poor
Svensson et al.	CCT	-	-	?	-	-	+	+	?	+	+	-	Questionable
Treacy et al.	CCT	-	-	?	?	?	+	?	?	+	+	-	Poor
Vadalà et al.	RCT	+	+	?	?	?	+	+	?	+	+	-	Good
Witvrouw et al.	CCT	-	-	?	-	?	+	+	+	+	+	+	Good

Legend:
RCT Randomized controlled trial
CCT Clinical controlled trial

Table 4 Risk of bias assessment of cohort and cross-sectional studies

Article	Study design	1	2	3	4	5	6	7	8	Accurate description rehabilitation	Ratio men - women	Total score
Ahlen et al.	RC	+	no	+	+	?	+	+	-	+	+	Good
Ali et al.	CS	+	no	+	+	?	?	-	?	+	-	Questionable
Biernat et al.	PC	-	no	-	-	?	?	?	-	+	+	Poor
Boszotta et al.	PC	-	no	+	+	?	?	?	-	-	?	Poor
Bryant et al.	CS	+	no	+	+	?	+	+	?	+	-	Good
Chapman et al.	CS	-	no	+	+	?	+	?	?	+	+	Questionable
Clark et al.	CS	+	no	+	+	?	+	?	?	-	+	Questionable
Czamara et al.	PC	+	no	+	+	?	+	+	?	+	+	Good
De Carlo et al. 1997	CS	-	no	-	+	?	?	?	-	+	?	Poor
De Carlo et al. 1999	CASE	+	no	-	+	?	+	+	?	+	-	Questionable
Eitzen et al.	PC	+	yes	+	+	?	+	+	+	+	-	Good
Hill et al.	PC	-	no	+	+	?	+	-	?	-	-	Poor
Howell et al.	PC	+	no	+	+	?	+	+	?	+	-	Good
Hui et al.	PC	+	yes	+	+	?	+	+	+	+	+	Good
Janssen et al. 2011	CS	+	no	+	+	?	+	+	+	+	?	Good
Janssen et al. 2013	PC	-	yes	+	+	?	+	+	+	+	-	Good
Kim et al.	RC	+	no	+	+	-	+	+	-	-	-	Questionable
Smith F et al.	CS	+	no	+	+	?	+	-	?	+	+	Good
Trojani et al.	RC	+	yes	+	+	?	+	+	?	+	-	Good
Zaffagnini et al.	PC	+	no	+	+	-	+	+	+	-	+	Good

Legend:
RC Retrospective cohort study
PC Propective cohort study
CS Cross-sectional study
CASE Case study

Table 5 Details rehabilitation

Rehabilitation	Preop rehab	ACL graft	Brace	Full weight-bearing allowed	FROM allowed	CKC exercises	OKC exercises	Concentric exercises	Eccentric exercises	Running	Return to light sports	Unrestricted return to sports	Criteria for return to sports
Ahlen et al. 2012	?	HS	no	immediate	immediate	immediate	6 wks	?	?	3 months	?	6 months	subjective functional stability compared to contralateral leg
Ali et al. 2006	?	HS	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	6 months	9 months	stable knee (Lachman and pivot test) and asymptomatic knee
Baltaci et al. 2013	?	HS	no	immediate	immediate	immediate	6-8 weeks	3-4 weeks	6-8 weeks?	3 months	6-8 months	6-8months	?
Beard et al. 2001	?	HS-PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	?	?
Bryant et al. 2007	?	PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	?	?
Chapman et al. 1995	?	PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	?	?
Christensen et al. 2013	?	HS	brace vs no brace	immediate (Program Biggs)	immediate	Program Biggs	Program Biggs	?	?	8-12 weeks	?	?	?
Clark et al. 2014	?	HS	no	immediate	immediate	?	?	?	?	3-4 months	?	?	?
Clatworthy et al. 1999	?	HS-PT	no	"accelerated rehabiliation protocol"	?	?	?	?	?	?	?	?	?
Corry et al. 1999	yes	HS-PT	no	immediate	immediate	immediate?	?	?	?	6 weeks	6 weeks	9 months	?
Czamara et al. 2014	?	HS	no	immediate	immediate	immediate	6-12 weeks?	6 weeks	6-12 weeks	4 months	?	?	?
de Carlo et al. 1999	yes	PT	no	immediate	immediate	immediate	2-6 weeks	2-6 weeks	2-6 weeks	6 weeks	5 weeks	6 weeks?	?
Eitzen et al. 2009	?	PT	no	immediate	immediate	2 weeks	5 weeks?	Program Risberg	Program Risberg	13 weeks	?	?	?
Ejerhed et al. 2003	?	HS-PT	no	immediate	immediate	immediate	6 weeks	?	?	3 months	?	6 months	full functional stability
Feller et al. 2003	?	HS-PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	6 months	Program Shelbourne	Program Shelbourne	10 weeks	6 months	9 months	?
Fukuda et al. 2013	?	HS	no	immediate	immediate	2 weeks	4 vs 12 weeks	?	?	10 weeks	?	?	?
Gerber et al. 2007&2009	?	HS-PT	no	PT immediate, HS 2-3 weeks?	immediate	immediate	5 weeks vs 7 weeks?	3 weeks	3 vs 15 weeks	?	?	?	90% strength and performance ability compared to uninvolved leg
Grant et al. 2010	?	PT	no	immediate	immediate	immediate	3 weeks	immediate	?	7-12 weeks	?	?	?
Heijne et al. 2007&2009	?	HS-PT	no	immediate	immediate	immediate	4 vs 12 weeks	?	?	4-6 months	?	6 months	functional capacity
Howell et al.	?	HS	no	immediate	immediate	4 weeks	4 weeks	?	?	8-10 weeks	?	4 months	?
Hui et al.	?	PT	no	immediate	immediate	immediate	?	?	?	6 weeks	?	6-9 months	?
Janssen et al. 2011&2013	yes	HS	no	immediate	immediate	immediate	6 weeks	6 weeks (start 90°-40°) 10 weeks (FROM)	6 weeks (start 90°-40°) 10 weeks (FROM)	10 weeks	4 months	4-6 months	?
Kim et al. 2014	?	PT	no	immediate	immediate	?	?	?	?	12 weeks	?	6 months	?
Kinikli et al. 2014	?	HS	no	immediate (Program Wilk/Majima)	immediate	immediate	6-8 weeks	3 weeks (study group)	3 weeks (study group)	?	?	?	?
Koutras et al. 2012	yes	HS	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	?	?
Laoruenthana e al. 2009	?	HS-PT	no	immediate (Program Howell)	immediate	4 weeks	4 weeks	?	?	?	?	9 months	no effusion, FROM
Mikkelsen et al. 2000	?	PT	no	immediate	immediate	2 weeks	6 weeks (study group)	6 weeks (start 90°-40°) 12 weeks (90°-10°)	6 weeks (start 90°-40°) 12 weeks (90°-10°)	3 months	?	?	?
Mohammadi et al. 2013	?	HS-PT	no	"accelerated rehabilitation protocol"	?	?	?	?	?	?	?	6-9 months	ability to do sports-related movements safely
Pinczewski et al. 2002&2009	?	HS-PT	no	immediate	immediate	6 weeks?	?	?	?	6 weeks	?	6 months	knee stability
Revenas et al. 2007	yes	HS-PT	no	immediate	immediate	immediate	6 weeks	?	?	?	?	?	?
Rudroff et al. 2003	?	HS-PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	3 months?	
Salmon et al. 2006	?	HS	no	immediate	immedate	immediate	?	?	?	6 weeks	?	6 months	rehabilitation goals met
Sastre et al. 2010	?	HS	no	immediate	immediate	?	?	?	?	12 weeks	?	6-9 months	?
Schenk et al. 1997	yes	PT	no	immediate	immediate	immediate	?	?	?	6 weeks	?	4-6 months	functional parameters (hop, swelling, patient satisfaction/confidence)
Shaarani et al. 2013	yes	PT	no	immediate	immediate					?	?	6 months	?
Smith et al. 2004	yes	HS-PT	no	immediate (Program Shelbourne)	immediate	Program Shelbourne	Program Shelbourne	Program Shelbourne	Program Shelbourne	?	?	?	?
Svensson et al. 2006	?	HS-PT	no	immediate	immediate	immediate	6 weeks	?	?	3 months	?	6 months	full functional stability
Trojani et al. 2009	?	HS	no	immediate	immediate	immediate	?	?	?	8 weeks	?	6 months	?
Vadalà et al. 2007	?	HS	brace vs no brace	immediate	immediate vs 2 weeks	immediate	?	?	?	3 months	?	?	?
Witvrouw et al. 2001	?	HS-PT	no	immediate	immediate	immediate	?	?	?	6 weeks	?	9 months	?
Zaffagnini et al. 2014	?	HS	no	immediate	immediate	immediate	?	?	?	2 months	?	4 months	criteria for on field rehabilitation, not for return to unrestricted sports

Legend:
HS hamstring autograft - *PT* patellar tendon autograft - *FROM* Full Range Of Motion - *CKC* Closed Kinetic Chain - *OKC* Open Kinetic Chain

References

1. Adams D, Logerstedt DS, Hunter-Giordano A, Axe MJ, Snyder-Mackler L (2012) Current concepts for anterior cruciate ligament reconstruction: a criterion-based rehabilitation progression. J Orthop Sports Phys Ther 42(7):601-614

2. Ahlen M, Liden M, Bovaller A, Sernert N, Kartus J (2012) Bilateral magnetic resonance imaging and functional assessment of the semitendinosus and gracilis tendons a minimum of 6 years after ipsilateral harvest for anterior cruciate ligament reconstruction. Am J Sports Med 40(8):1735-1741

3. Ali MS, Kumar A, Adnaan Ali S, Hislop T (2006) Anterior cruciate ligament reconstruction using hamstring tendon graft without detachment of the tibial insertion. Arch Orthop Trauma Surg 126(9):644-648

4. Andersson D, Samuelsson K, Karlsson J (2009) Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials. Arthroscopy 25(6):653-685

5. Ardern CL, Webster KE, Taylor NF, Feller JA (2011) Return to sport following anterior cruciate ligament reconstruction surgery: a systematic review and meta-analysis of the state of play. Br J Sports Med 45(7):596-606

6. Ardern CL, Taylor NF, Feller JA, Webster KE (2012) Return-to-sport outcomes at 2 to 7 years after anterior cruciate ligament reconstruction surgery. Am J Sports Med 40(1):41-48

7. Ardern CL, Taylor NF, Feller JA, Webster KE (2014) Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 48(21):1543-1552

8. Baltaci G, Harput G, Haksever B, Ulusoy B, Ozer H (2013) Comparison between Nintendo Wii Fit and conventional rehabilitation on functional performance outcomes after hamstring anterior cruciate ligament reconstruction: prospective, randomized, controlled, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc 21(4):880-887

9. Barber-Westin SD, Noyes FR (2011) Objective criteria for return to athletics after anterior cruciate ligament reconstruction and subsequent reinjury rates: a systematic review. Phys Sportsmed 39(3):100-110

10. Barber-Westin SD, Noyes FR (2011) Factors used to determine return to unrestricted sports activities after anterior cruciate ligament reconstruction. Arthroscopy 27(12):1697-1705

11. Beard DJ, Anderson JL, Davies S, Price AJ, Dodd CAF (2001) Hamstrings vs. patella tendon for anterior cruciate ligament reconstruction: A randomised controlled trial. Knee 8(1):45-50

12. Beynnon BD, Fleming BC, Johnson RJ, Nichols CE, Renstrom PE, Pope MH (1995) Anterior cruciate ligament strain behavior during rehabilitation exercises in vivo... presented at the joint meeting of the International Society of the Knee/International Arthroscopy Association of America, Copenhagen, Denmark, June 27, 1993. Am J Sports Med 23(1):24-34

13. Beynnon BD, Johnson RJ, Fleming BC, Stankewich CJ, Renstrom PA, Nichols CE (1997) The strain behavior of the anterior cruciate ligament during squatting and active flexion-extension: a comparison of an open and a closed kinetic chain exercise. Am J Sports Med 25(6):823-829

14. Beynnon BD, Johnson RJ, Naud S, Fleming BC, Abate JA, Brattbakk B, Nichols CE (2011) Accelerated versus nonaccelerated rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind investigation evaluating knee joint laxity using roentgen stereophotogrammetric analysis. Am J Sports Med 39(12):2536-2548

15. Biernat R, Wolosewicz M, Tomaszewski W (2007) A protocol of rehabilitation after ACL reconstruction using a hamstring autograft in the first month after surgery-a preliminary report. Ortop Traumatol Rehabil 9(2):178-186

16. Biggs A, Jenkins WL, Urch SE, Shelbourne KD (2009) Rehabilitation for patients following ACL reconstruction: a knee symmetry model. N Am J Sports Phys Ther 4(1): 2-12

17. Boszotta H (2003) Arthroscopic reconstruction of anterior cruciate ligament using BTB patellar ligament in the press-fit technique. Surg Technol Int 11:249-253

18. Bryant AL, Kelly J, Hohmann E (2008) Neuromuscular adaptations and correlates of knee functionality following ACL reconstruction. J Orthop Res 26(1):126-135

19. Chapman A, Chamberlain V, Railton R, Boyle J, Strauss G (1995) Extensor strength in the anterior cruciate reconstructed knee. Austral J Phys 41(2):83-88

20. Christensen JC, Goldfine LR, West HS (2013) The effects of early aggressive rehabilitation on outcomes after anterior cruciate ligament reconstruction using autologous hamstring tendon: a randomized clinical trial. J Sport Rehabil 22(3):191-201

21. Claes S, Verdonk P, Forsyth R, Bellemans J (2011) The "ligamentization" process in anterior cruciate ligament reconstruction: what happens to the human graft? A systematic review of the literature. Am J Sports Med 39(11):2476-2483

22. Clark RA, Howells B, Feller J, Whitehead T, Webster KE (2014) Clinic-based assessment of weight-bearing asymmetry during squatting in people with anterior cruciate ligament reconstruction using Nintendo Wii Balance Boards. Arch Phys Med Rehabil 95(6):1156-1161

23. Clatworthy MG, Annear P, Bulow JU, Bartlett RJ (1999) Tunnel widening in anterior cruciate ligament reconstruction: a prospective evaluation of hamstring and patella tendon grafts. Knee Surg Sports Traumatol Arthrosc 7(3):138-145

24. Corry IS, Webb JM, Clingeleffer AJ, Pinczewski LA (1999) Arthroscopic reconstruction of the anterior cruciate ligament: a comparison of patellar tendon autograft and four-strand hamstring tendon autograft. Am J Sports Med 27(4):444-454

25. Czamara A, Krolikowska A, Szuba L, Widuchowski W, Kentel M (2015) Single- versus double-bundle anterior cruciate ligament reconstruction: a new aspect of knee assessment during activities involving dynamic knee rotation. J Strength Cond Res 29(2):489–499

26. De Carlo M, Klootwyk TE, Shelbourne KD (1997) ACL surgery and accelerated rehabilitation: revisited. J Sport Rehabil 6(2):144-156

27. De Carlo M, Shelbourne KD, Oneacre K (1999) Rehabilitation program for both knees when the contralateral autogenous patellar tendon graft is used for primary anterior cruciate ligament reconstruction: a case study. J Orthop Sports Phys Ther 29(3):144-153; discussion 154-149

28. Eitzen I, Holm I, Risberg MA (2009) Preoperative quadriceps strength is a significant predictor of knee function two years after anterior cruciate ligament reconstruction. Br J Sports Med 43(5):371-376

29. Ejerhed L, Kartus J, Sernert N, Kohler K, Karlsson J (2003) Patellar tendon or semitendinosus tendon autografts for anterior cruciate ligament reconstruction? A prospective randomized study with a two-year follow-up. Am J Sports Med 31(1):19-25

30. Engelen-van Melick N, van Cingel RE, Tijssen MP, Nijhuis-van der Sanden MW (2013) Assessment of functional performance after anterior cruciate ligament reconstruction: a systematic review of measurement procedures. Knee Surg Sports Traumatol Arthrosc 21(4):869-879

31. Escamilla RF, Macleod TD, Wilk KE, Paulos L, Andrews JR (2012) Anterior cruciate ligament strain and tensile forces for weight-bearing and non-weight-bearing exercises: a guide to exercise selection. J Orthop & Sports Phys Ther 42(3):208-220

32. Feller JA, Webster KE (2003) A randomized comparison of patellar tendon and hamstring tendon anterior cruciate ligament reconstruction. Am J Sports Med 31(4):564-573

33. Fukuda TY, Fingerhut D, Moreira VC, Camarini PM, Scodeller NF, Duarte A, Jr., Martinelli M, Bryk FF (2013) Open kinetic chain exercises in a restricted range of motion after anterior cruciate ligament reconstruction: a randomized controlled clinical trial. Am J Sports Med 41(4):788-794

34. Gerber JP, Marcus RL, Dibble LE, Greis PE, Burks RT, LaStayo PC (2007) Effects of early progressive eccentric exercise on muscle structure after anterior cruciate ligament reconstruction. J Bone Joint Surg Am 89(3):559-570

35. Gerber JP, Marcus RL, Dibble LE, Greis PE, Burks RT, LaStayo PC (2009) Effects of early progressive eccentric exercise on muscle size and function after anterior cruciate ligament reconstruction: a 1-year follow-up study of a randomized clinical trial. Phys Ther 89(1):51-59

36. Grant JA, Mohtadi NG (2010) Two- to 4-year follow-up to a comparison of home versus physical therapy-supervised rehabilitation programs after anterior cruciate ligament reconstruction. Am J Sports Med 38(7):1389-1394

37. Han DL, Nyland J, Kendzior M, Nawab A, Caborn DN (2012) Intratunnel versus extratunnel fixation of hamstring autograft for anterior cruciate ligament reconstruction. Arthroscopy 28(10):1555-1566

38. Harris JD, Abrams GD, Bach BR, Williams D, Heidloff D, Bush-Joseph CA, Verma NN, Forsythe B, Cole BJ (2014) Return to sport after ACL reconstruction. Orthopedics 37(2):e103-108

39. Heijne A, Werner S (2007) Early versus late start of open kinetic chain quadriceps exercises after ACL reconstruction with patellar tendon or hamstring grafts: a prospective randomized outcome study.
Knee Surg Sports Traumatol Arthrosc 15(4):402–414

40. Heijne A, Werner S (2010) A 2-year follow-up of rehabilitation after ACL reconstruction using patellar tendon or hamstring tendon grafts: a prospective randomised outcome study. Knee Surg Sports Traumatol Arthrosc 18(6):805–813

41. Herbst E, Hoser C, Hildebrandt C, Raschner C, Hepperger C, Pointner H, Fink C (2015) Functional assessments for decision-making regarding return to sports following ACL reconstruction. Part II: clinical application of a new test battery.
Knee Surg Sports Traumatol Arthrosc 23(5):1283–1291

42. Hill GN, O'Leary ST (2013) Anterior cruciate ligament reconstruction: the short-term recovery using the Knee Injury and Osteoarthritis Outcome Score (KOOS).
Knee Surg Sports Traumatol Arthrosc 21(8):1889–1894

43. Howell SM, Taylor MA (1996) Brace-free rehabilitation, with early return to activity, for knees reconstructed with a double-looped semitendinosus and gracilis graft.
J Bone Joint Surg Am 78(6):814–825

44. Hui C, Salmon LJ, Kok A, Maeno S, Linklater J, Pinczewski LA (2011) Fifteen-year outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft for "isolated" anterior cruciate ligament tear. Am J Sports Med 39(1):89–98

45. Janssen RP, Scheffler SU (2014) Intra-articular remodelling of hamstring tendon grafts after anterior cruciate ligament reconstruction.
Knee Surg Sports Traumatol Arthrosc 22(9):2102–2108

46. Janssen RP, Velden van der MJ, Pasmans HL, Sala HA (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction.
Knee Surg Sports Traumatol Arthrosc 21(4):898–905

47. Janssen RP, du Mée AW, van Valkenburg J, Sala HA, Tseng CM (2013) Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. Knee Surg Sports Traumatol Arthrosc 21(9):1977–1988

48. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299–1306

49. Kim HS, Seon JK, Jo AR (2013) Current trends in anterior cruciate ligament reconstruction. Knee Surg Relat Res 25(4):165–173

50. Kim SJ, Lee SK, Kim SH, Kim SH, Kim JS, Jung M (2014) Does anterior laxity of the uninjured knee influence clinical outcomes of ACL reconstruction?
J Bone Joint Surg Am 96(7):543–548

51. Kinikli GI, Yuksel I, Baltaci G, Atay OA (2014) The effect of progressive eccentric and concentric training on functional performance after autogenous hamstring anterior cruciate ligament reconstruction: a randomized controlled study.
Acta Orthop Traumatol Turc 48(3):283–289

52. Koutras G, Papadopoulos P, Terzidis IP, Gigis I, Pappas E (2013) Short-term functional and clinical outcomes after ACL reconstruction with hamstrings autograft: transtibial versus anteromedial portal technique.
Knee Surg Sports Traumatol Arthrosc 21(8):1904–1909

53. Kruse LM, Gray B, Wright RW (2012) Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. J Bone Joint Surg Am 94(19):1737–1748

54. Laoruengthana A, Pattayakorn S, Chotanaputhi T, Kosiyatrakul A (2009) Clinical comparison between six-strand hamstring tendon and patellar tendon autograft in arthroscopic anterior cruciate ligament reconstruction: a prospective, randomized clinical trial. J Med Assoc Thai 92(4):491–497

55. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62(10):e1–34

56. Majima T, Yasuda K, Tago H, Tanabe Y, Minami A (2002) Rehabilitation after hamstring anterior cruciate ligament reconstruction. Clin Orthop Relat Res(397):370–380

57. Marumo K, Saito M, Yamagishi T, Fujii K (2005) The "ligamentization" process in human anterior cruciate ligament reconstruction with autogenous patellar and hamstring tendons: a biochemical study. Am J Sports Med 33(8):1166–1173

58. Melikoglu MA, Balci N, Samanci N, Filiz MB, Gurbuz U, Dagseven T, Ozenci AM, Gur S (2008) Timing of surgery and isokinetic muscle performance in patients with anterior cruciate ligament injury. J Back and Musculoskel Rehab 21(1):23–28

59. Menetrey J, Duthon VB, Laumonier T, Fritschy D (2008) "Biological failure" of the anterior cruciate ligament graft. Knee Surg Sports Traumatol Arthrosc 16(3):224–231

60. Middleton KK, Hamilton T, Irrgang JJ, Karlsson J, Harner CD, Fu FH (2014) Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1.
Knee Surg Sports Traumatol Arthrosc 22(7):1467–1482

61. Mikkelsen C, Werner S, Eriksson E (2000) Closed kinetic chain alone compared to combined open and closed kinetic chain exercises for quadriceps strengthening after anterior cruciate ligament reconstruction with respect to return to sports: a prospective matched follow-up study. Knee Surg Sports Traumatol Arthrosc 8(6):337–342

62. Mohammadi F, Salavati M, Akhbari B, Mazaheri M, Mohsen Mir S, Etemadi Y (2013) Comparison of functional outcome measures after ACL reconstruction in competitive soccer players: a randomized trial. J Bone Joint Surg Am 95(14):1271–1277

63. Muller B, Bowman KF, Jr., Bedi A (2013) ACL graft healing and biologics.
Clin Sports Med 32(1):93–109

64. Nyland J, Brand E, Fisher B (2010) Update on rehabilitation following ACL reconstruction. Open Access J Sports Med 1:151–166

65. Pauzenberger L, Syre S, Schurz M (2013) "Ligamentization" in hamstring tendon grafts after anterior cruciate ligament reconstruction: a systematic review of the literature and a glimpse into the future. Arthroscopy 29(10):1712–1721

66. Pinczewski LA, Deehan DJ, Salmon LJ, Russell VJ, Clingeleffer A (2002) A five-year comparison of patellar tendon versus four-strand hamstring tendon autograft for arthroscopic reconstruction of the anterior cruciate ligament.
Am J Sports Med 30(4):523–536

67. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J (2007) A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial.
Am J Sports Med 35(4):564–574

68. Renstrom PA (2013) Eight clinical conundrums relating to anterior cruciate ligament (ACL) injury in sport: recent evidence and a personal reflection.
Br J Sports Med 47(6):367–372

69. Revenäs A, Johansson A, Leppert J (2009) A randomized study of two physiotherapeutic approaches after knee ligament reconstruction. Adv in Phys 11(1): 30–41

70. Risberg MA, Holm I, Myklebust G, Engebretsen L (2007) Neuromuscular training versus strength training during first 6 months after anterior cruciate ligament reconstruction: a randomized clinical trial. Phys Ther 87(6):737–750

71. Rudroff T (2003) Functional capability is enhanced with semitendinosus than patellar tendon ACL repair. Med Sci Sports Exerc 35(9):1486–1492

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

73. Samuelsson K, Andersson D, Ahlden M, Fu FH, Musahl V, Karlsson J (2013) Trends in surgeon preferences on anterior cruciate ligament reconstructive techniques.
Clin Sports Med 32(1):111–126

74. Sastre S, Popescu D, Nunez M, Pomes J, Tomas X, Peidro L (2010) Double-bundle versus single-bundle ACL reconstruction using the horizontal femoral position: a prospective, randomized study. Knee Surg Sports Traumatol Arthrosc 18(1):32–36

75. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction.
Knee Surg Sports Traumatol Arthrosc 16(9):834–842

76. Schenck RC, Jr., Blaschak MJ, Lance ED, Turturro TC, Holmes CF (1997) A prospective outcome study of rehabilitation programs and anterior cruciate ligament reconstruction. Arthroscopy 13(3):285–290

77. Shaarani SR, O'Hare C, Quinn A, Moyna N, Moran R, O'Byrne JM (2013) Effect of prehabilitation on the outcome of anterior cruciate ligament reconstruction.
Am J Sports Med 41(9):2117–2127

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

79. Shelbourne KD, Foulk DA (1995) Timing of surgery in acute anterior cruciate ligament tears on the return of quadriceps muscle strength after reconstruction using an autogenous patellar tendon graft. Am J Sports Med 23(6):686–689

80. Shelbourne KD, Klotz C (2006) What I have learned about the ACL: utilizing a progressive rehabilitation scheme to achieve total knee symmetry after anterior cruciate ligament reconstruction. J Orthop Sci 11(3):318–325

81. Shelbourne KD, Klootwyk TE, Decarlo MS (1992) Update on accelerated rehabilitation after anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 15(6): 303–308

82. Shelbourne KD, Vanadurongwan B, Gray T (2007) Primary anterior cruciate Ligament reconstruction using contralateral patellar tendon autograft. Clin Sports Med 26(4):549–565

83. Slavin RE (1995) Best evidence synthesis: an intelligent alternative to meta-analysis. J Clin Epidemiol 48(1):9–18

84. Smith FW, Rosenlund EA, Aune AK, MacLean JA, Hillis SW (2004) Subjective functional assessments and the return to competitive sport after anterior cruciate ligament reconstruction. Br J Sports Med 38(3):279–284

85. Svensson M, Sernert N, Ejerhed L, Karlsson J, Kartus JT (2006) A prospective comparison of bone-patellar tendon-bone and hamstring grafts for anterior cruciate ligament reconstruction in female patients. Knee Surg Sports Traumatol Arthrosc 14(3):278–286

86. Tohyama H, Yoshikawa T, Ju YJ, Yasuda K (2009) Revascularization in the tendon graft following anterior cruciate ligament reconstruction of the knee: its mechanisms and regulation. Chang Gung Med J 32(2):133–139

87. Treacy SH, Barron OA, Brunet ME, Barrack RL (1997) Assessing the need for extensive supervised rehabilitation following arthroscopic ACL reconstruction. Am J Orthop (Belle Mead NJ) 26(1):25–29

88. Trojani C, Sane JC, Coste JS, Boileau P (2009) Four-strand hamstring tendon autograft for ACL reconstruction in patients aged 50 years or older. Orthop Traumatol Surg Res 95(1):22–27

89. Vadala A, Iorio R, De Carli A, Argento G, Di Sanzo V, Conteduca F, Ferretti A (2007) The effect of accelerated, brace-free, rehabilitation on bone tunnel enlargement after ACL reconstruction using hamstring tendons: a CT study. Knee Surg Sports Traumatol Arthrosc 15(4):365–371

90. van Eck CF, Schreiber VM, Mejia HA, Samuelsson K, van Dijk CN, Karlsson J, Fu FH (2010) "Anatomic" anterior cruciate ligament reconstruction: a systematic review of surgical techniques and reporting of surgical data. Arthroscopy 26(9 Suppl):S2–12

91. van Grinsven S, van Cingel RE, Holla CJ, van Loon CJ (2010) Evidence-based rehabilitation following anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 18(8):1128–1144

92. van Tulder M, Furlan A, Bombardier C, Bouter L, Editorial Board of the Cochrane Collaboration Back Review G (2003) Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine (Phila Pa 1976) 28(12):1290–1299

93. Walden M, Hagglund M, Magnusson H, Ekstrand J (2011) Anterior cruciate ligament injury in elite football: a prospective three-cohort study. Knee Surg Sports Traumatol Arthrosc 19(1):11–19

94. Warner SJ, Smith MV, Wright RW, Matava MJ, Brophy RH (2011) Sport-specific outcomes after anterior cruciate ligament reconstruction. Arthroscopy 27(8): 1129–1134

95. Wilk KE, Reinold MM, Hooks TR (2003) Recent advances in the rehabilitation of isolated and combined anterior cruciate ligament injuries. Orthop Clin North Am 34(1):107–137

96. Witvrouw E, Bellemans J, Verdonk R, Cambier D, Coorevits P, Almqvist F (2001) Patellar tendon vs. doubled semitendinosus and gracilis tendon for anterior cruciate ligament reconstruction. Int Orthop 25(5):308–311

97. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part II: open versus closed kinetic chain exercises, neuromuscular electrical stimulation, accelerated rehabilitation, and miscellaneous topics. J Knee Surg 21(3):225–234

98. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part I: continuous passive motion, early weight bearing, postoperative bracing, and home-based rehabilitation. J Knee Surg 21(3):217–224

99. Yabroudi MA, Irrgang JJ (2013) Rehabilitation and return to play after anatomic anterior cruciate ligament reconstruction. Clin Sports Med 32(1):165–175

100. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Tsapralis K, Ricci M, Bragonzoni L, Della Villa S, Marcacci M (2014) Return to sport after anterior cruciate ligament reconstruction in professional soccer players. Knee 21(3):731–735

PREDICTION OF LENGTH AND DIAMETER OF HAMSTRING TENDON AUTOGRAFTS FOR KNEE LIGAMENT SURGERY IN CAUCASIANS

Rob P.A. Janssen, Maria J.F. van der Velden,
Marijn van den Besselaar, Max Reijman

Knee Surgery, Sports Traumatology, Arthroscopy 2015 Jun 28 [Epub ahead of print]
DOI 10.1007/s00167-015-3678-5

Abstract

Purpose
Prediction of hamstring tendon autograft size facilitates preoperative planning of knee ligament surgery and may reduce the need for allografts in complex knee reconstructions. The aim of this study was to analyse whether length and diameter of hamstring tendon autografts can be predicted preoperatively with anthropometric parameters and patient characteristics.

Methods
In this observational study, 725 consecutive Caucasian patients scheduled for ACL reconstruction were included. Preoperatively gender, age, height and weight were recorded. After harvest, tendon lengths of both gracilis- and semitendinosus tendons were measured. Diameter of the final 4-strand hamstring autograft was recorded. Relationship between length and diameter of tendon grafts and different anthropometric parameters were assessed by linear and logistic regression analyses.

Results
Mean lengths of the semitendinosus and gracilis tendon autografts were 28.9 ± 3.1 cm and 27.7 ± 3.0 cm respectively. Length of the gracilis and semitendinosus grafts was independently related to patient height. Female gender was correlated with smaller graft diameter. One in nine female patients had a diameter < 8 mm. The ratio in men was 1 in 36.

Conclusion
Hamstring autograft length and size can be predicted in Caucasians. Length of the gracilis and semitendinosus tendons was related to patient height. Smaller graft diameter was related to female gender.

Keywords
Hamstring · Tendon · Autograft · Length · Diameter · Knee ligament reconstruction · ACL · Multiligament

Level of evidence II

Introduction

Hamstring tendon autografts have become increasingly popular for knee ligament reconstructions.[22] In 2012, 95% of the primary anterior cruciate ligament (ACL) reconstructions in Sweden were performed with hamstring tendon autografts.[14] In a recent review, Samuelsson et al. stated that hamstring tendons, compared to bone–patella tendon–bone autografts, put the surgical skills of the orthopaedic surgeon to test because it is not possible to preoperatively assess the graft dimensions of the tendon.[30]

Complex knee ligament reconstructions require specific tendon length and diameter depending on the fixation method, graft preparation technique and type of reconstruction.[6, 7, 11, 15, 20, 21, 25]
The question arises whether the hamstring tendon autograft will be of sufficient length and diameter for knee ligament surgery. Various authors have analysed the predictability of hamstring tendon dimensions by anthropometric parameters.[2, 4, 5, 10, 16, 18, 24–27, 29, 31, 32, 35–38]

Some studies analysed graft diameter.[2, 4, 18, 25, 27, 35, 37] Studies that focused on hamstring tendon length used small study populations or human cadavers.[5, 10, 16, 24, 26, 29, 31, 32, 36] Only Xie et al. studied a larger population of 235 Chinese Han patients.[38] Hamstring tendon length appears to be longer in Caucasian patients in comparison with Chinese patients.[5] Length of hamstring tendon autografts has not been studied in a large Caucasian population.

Prediction of length and diameter of hamstring tendon autografts is clinically useful. It may reduce the need for expensive allografts in complex knee ligament surgery.[8, 23] Autografts enhance the quality of reconstructions with regard to graft rupture and knee stability compared to allografts.[1, 3, 9, 13, 19, 28, 33] Furthermore, prediction of hamstring autograft tendon dimension is beneficiary for complex knee ligament reconstructions in countries where allografts are not available.

The primary aim of the present study is to analyse the preoperative predictability of hamstring tendon length and diameter with anthropometric parameters and patient characteristics in a large Caucasian population. The hypothesis is that length and diameter of hamstring tendon autografts can be predicted by anthropometric parameters.

Materials and methods

In this observational study, 725 consecutive Caucasian patients with ACL rupture, scheduled for ACL reconstruction between October 2007 and January 2014, were eligible for inclusion. All patients undergoing primary or revision ACL reconstruction with 4–strand hamstring tendon autografts were included. Exclusion criteria were ACL reconstruction with other auto– or allografts, previous ipsilateral hamstring tendon harvest, previous limb amputation or congenital limb deficiency that would affect total body weight, neuromuscular disorders and non–Caucasian race.

Preoperatively gender, age, height and weight were recorded. Two orthopaedic surgeons (RJ and MB) performed all procedures using the same hamstring tendon harvesting technique. Both gracilis and semitendinosus tendons were harvested for ACL reconstruction. The hamstring tendon harvesting technique has been described in detail in a previous publication.[12]

Both tendons were prepared in a standardized fashion as a 4–strand ACL graft. Muscle tissue was removed from the tendon. The available length of each tendon was measured with a ruler and recorded in cm, rounded off to the nearest 0.5 cm. Each tendon end was sutured with a no. 1 absorbable suture. The diameter of the 4–strand hamstring graft was measured by sizing tubes (Biomet, Warsaw, IN, USA) calibrated to 1 mm, range 7 to 9 mm.

The correlation was evaluated between length and diameter of harvested hamstring tendons and gender, age, height and weight of the patient.

The study was approved by an independent medical ethical committee (METC 2014–30; Máxima Medical Centre, Eindhoven, The Netherlands).

Statistical Analysis
Linear regression analyses were used to analyse the predictability of hamstring tendon autograft length. For the diameter of hamstring tendon autografts (cut–off point of < 8 mm), logistic regression analyses were performed.

Length of the hamstring tendon autografts and diameter of the 4–strand ACL grafts were used as dependent variables, the anthropometric parameters and patient characteristics as independent variables. Univariate and multivariate analyses were performed by the enter method. The following anthropometric parameters and patient characteristics were analysed: gender, age, height and weight.

Most current knee ligament reconstructions require graft lengths of 20–28 cm.[11, 15, 17] Therefore, tendon length cut–off points of 21 cm and 28 cm were determined. Predictability of hamstring tendon autograft length of < 21 cm and < 28 cm was analysed by assessing the abovementioned anthropometric parameters and patient characteristics. Significance was set at ≤ 0.05 in all analyses. IBM SPSS Statistics version 19.0 (IBM, Armonk, New York) was used for statistical analysis.

Results

Baseline characteristics of the study population are shown in Table 1. Eighteen patients had missing data (respectively height, weight, gracilis length, semitendinosus length, and graft diameter in 8, 11, 4, 2, and 2 patients). Some patients had more than one missing value.

Mean lengths of the semitendinosus and gracilis tendon autograft were 28.9 ± 3.1 standard deviation (SD) cm and 27.7 ± 3.0 cm SD respectively. Two patients (0.3%) had a semitendinosus tendon length shorter than 21 cm. Twelve patients (1.7%) had gracilis tendons shorter than 21 cm. A total of 42 patients (5.8%) had graft diameters ≤ 7 mm, 359 patients (49.7%) had graft diameters of 8 mm, and 322 patients (44.5%) diameters ≥ 9 mm.

Length of both the gracilis and semitendinosus tendon was correlated to patient height (Table 2). A regression coefficient of 0.16 signifies that an increase of 1 cm of patient height is correlated with an increase of 0.16 cm of gracilis length. Because of the limited number of patients with tendon autografts < 21 cm, assessment of the relationship between this cut–off point and anthropometric parameters and patient characteristics was not performed. With regard to tendon lengths < 28 cm, shorter patients more frequently had gracilis and semitendinosus tendon autografts < 28 cm (Table 3).

A correlation was found between gender and graft diameter < 8 mm (Table 4). Table 5 shows that women more often had a graft diameter < 8 mm in comparison with men.

Discussion

The most important finding of the present study is that length and diameter of hamstring tendon autografts can be predicted by anthropometric parameters in patients of Caucasian race. Length of gracilis and semitendinosus tendons was independently related to patient height. Smaller graft diameter was independently related to female gender.

Hamstring autograft length prediction
In the present study, hamstring tendon length of both semitendinosus and gracilis autograft tendons was correlated to patient height. A similar correlation was found by other studies with smaller and/or non–Caucasian populations.[5, 10, 24, 29, 32, 36, 38]
Chiang et al.[5] studied a group of 100 Chinese patients and found a significant correlation between height and length of both semitendinosus and gracilis tendons after multiple linear regression analysis. The authors compared their data to the study population by Treme et al.[36] and concluded that Caucasian patients had significantly longer hamstring tendons compared to the Chinese Han population.[5] This conclusion on racial difference by Chiang et al.[5] may be questionable since Treme et al. did not specify the race of their 50 consecutive patients.[36]

Xie et al.[38] concluded that height and weight were the best predictors for hamstring tendon length in men, whereas only height was a predictor in women. Analysis was by simple linear regression.[38] Although the present study showed weight to be a predictor for semitendinosus and gracilis tendon length in a univariate logistic regression analysis, this relationship was explained by patient height as demonstrated in the multivariate logistic regression analysis.

Gender has been associated with hamstring graft length.[36, 38] Xie et al. described that women had significantly shorter hamstring tendons than men.[38] Treme et al. found that women had significantly smaller and shorter grafts compared to men.[36] Other authors have confirmed these findings.[5, 24] The present study found gender to be a predictor of semitendinosus and gracilis tendon length in the univariate logistic regression analysis. However, this relationship can also be explained by patient height. Strength of the present study is the large sample size and level of statistical analysis. This may explain the variance in significance found in the literature for anthropometric predictors of graft length.

Current anatomic ACL reconstructions and fixation techniques allow the use of multiple-stranded hamstring autografts with a minimal tendon length of 21 cm.[17] Pichler et al.[26] studied the length of harvested hamstring tendons. The shortest harvested semitendinosus tendon was at least 20 cm long and 11% of gracilis tendons were shorter than 20 cm.[26] Leg length was the only anthropometric parameter in their cadaveric study. In contrast, the present study demonstrated that only 2 patients (0.3%) had semitendinosus tendon length < 21 cm. The gracilis tendon length was < 21 cm in 12 patients (1.7%). Hamstring tendon length was predictable, and almost always of sufficient length (≥ 21 cm) for ACL and MPFL reconstructions in a Caucasian population.[11, 17]

Longer grafts may be necessary for complex knee ligament surgery.[15, 17] Papastergiou et al.[24] analysed the predictability of semitendinosus tendon length by anthropometric parameters. Seventy-nine percent of harvested semitendinosus tendons were ≥ 28 cm. However, length of semitendinosus tendons was < 28 cm in 43.8% of female patients. Patients shorter than 167 cm were at highest risk for semitendinosus tendons < 28 cm.[24] This is comparable to the results of the present study; height ≥ 170 cm showed a greater probability of semitendinosus and/or gracilis tendons ≥ 28 cm. The comparable patient height in both studies (176.3 ± 8 cm[24] and 177.3 ± 9 cm respectively) could explain these similar results. The present study showed that hamstring tendon length was predictable for complex knee ligament surgery in Caucasians.

Hamstring autograft diameter prediction

The present study has shown that the diameter of a 4-strand hamstring tendon autograft is significantly correlated to gender. One in nine female patients had a diameter < 8 mm. The ratio in men was 1 in 36. The correlation between gender and graft diameter has been described in previous studies.[2, 18, 25-27, 35-38]

Park et al. concluded that graft diameter < 8 mm led to significantly more failures.[25] In younger patients, higher failure rates of ACL reconstructions with graft diameter ≤ 8 mm have been described.[20, 21] In the present study, graft diameter was < 8 mm in 2.8% of men and 11.3% of women. In contrast, Ma et al. found graft diameter < 8 mm in 18.4% of men and 42.3% of women.[18] Pinheiro et al. also described a larger percentage of graft diameters < 8 mm compared to the present study (18.5% of men and 66.7% of women).[27] These authors also used a 4-strand hamstring tendon autograft. However, it should be noted that mean patient height in the studies by Ma et al.[18] and Pinheiro et al.[27] was shorter in comparison to the present study (167.3 ± 4 cm, 170.0 ± 10 cm and 177.3 ± 9 cm respectively). This difference in height could explain the differences in graft diameter between the studies.

Ma et al. also correlated height to graft diameter in a multivariate regression analysis.[18] Men had significantly larger grafts than women (8.1 ± 0.8 vs 7.5 ± 0.6 mm respectively). Height was a specific predictor solely in men. In women, none of the preoperative measures were predictors for graft diameter.[18] Similarly, Papastergiou et al.[24] did not find any significant predictor for graft diameter in women. In their retrospective study of 61 consecutive patients (46 men, 16 women), the definition of adequate size graft was ≥ 7mm. The majority of patients (90%) had adequate grafts, only 10% of patients had grafts < 7 mm. Stratified for gender, 25% (all women) had graft sizes < 7 mm. Women were significantly shorter and lighter than men. Their hamstring grafts were also shorter with smaller diameters compared to men.[24] In the present study, adequate graft diameter was defined as ≥ 8 mm. Therefore, the results of the present study cannot be compared to the data by Papastergiou et al.[24] Other authors have confirmed the correlation between height and graft diameter.[4, 18, 24, 25, 27, 32, 35, 37, 38]

Several authors have described correlations between graft diameter and body weight [31, 35, 37, 38] and leg-length.[31] In these studies however, statistical limitations, small sample sizes and odd women to men ratios may explain the different predictors for graft diameter compared to the present study. In the latter, univariate linear regression analysis showed that gender, height and weight were significantly correlated to graft diameter. However, only gender was correlated to graft diameter after multivariate linear regression analysis in this large Caucasian population.

There are several limitations to the present study. Leg length was not measured and could not be used as parameter to predict autograft tendon length. Another limitation was the missing data in 18 patients. Furthermore, height and weight were not specifically measured but self-reported by patients. This could limit the accuracy of the measurements. Nevertheless, Spencer et al. assessed the validity of self-reported height and weight by comparison with measured height and weight and concluded that self-reported data are valid for identifying relationships in epidemiological studies.[34] The harvest technique in the study could have left a remnant tendon part after harvest. Pichler et al. researched this possible phenomenon in a cadaver study and concluded that insufficient tendon length was mainly caused by anatomical variations rather than tendon harvesting technique.[26] Another limitation of the present study is the fact that ACL reconstruction only allowed sizing by 1 mm intervals instead of 0.5 mm intervals. This might have led to an overestimation of the amount of larger diameter grafts.

The clinical relevance of the present study is that prediction of hamstring tendon length and graft diameter allows better preoperative planning for complex knee ligament surgery and may reduce the necessity of allografts. This reduces surgical costs[8, 23] and increases the quality of ligament reconstructions with regard to possible graft rupture and postoperative stability.[1, 3, 9, 13, 19, 28, 33] Furthermore, knee ligament reconstructions may be performed with greater confidence in countries where allografts are not available.

Conclusion

Length and diameter of hamstring autograft tendons can be predicted by anthropometric parameters in Caucasians. Length of gracilis and semitendinosus tendons is related to patient height. Smaller graft diameter is related to female gender.

Table 1 Patient characteristics

	Total (*n* = 725)
Age (year)	28.7 (±10.6)
Gender [% female (*n*)]	35.4 (257)
Weight (kg)	76.5 (±13.4)
Height (cm)	177.3 (±9)
BMI (kg/m²)	24.3 (±3.5)

Data are presented as mean (standard deviation), unless otherwise indicated
n number, *BMI* body mass index

Table 2 Predictors of tendon length

	Univariate			Multivariate		
	Regr. co.	(95 % CI)	*P* value	Regr. co.	(95 % CI)	*P* value
Gracilis						
Age	−0.01	(−0.03; 0.01)	n.s.	–	–	–
Gender (female)	−1.9	(−2.3; −1.4)	<0.001	0.06	(−0.49; 0.62)	n.s.
Weight	0.06	(0.04; 0.07)	<0.001	−0.005	(−0.02; 0.01)	n.s.
Height	0.15	(0.13; 0.17)	<0.001	0.16	(0.13; 0.19)	<0.001
Semitendinosus						
Age	−0.01	(−0.03; 0.01)	n.s.	–	–	–
Gender (female)	−2.4	(−2.8; −1.9)	<0.001	−0.03	(−0.55; 0.49)	n.s.
Weight	0.07	(0.06; 0.09)	<0.001	−0.01	(−0.02; 0.01)	n.s.
Height	0.19	(0.17; 0.21)	<0.001	0.20	(0.17; 0.23)	<0.001

Regr. co. regression coefficients, *95 % CI* 95 % confidence interval, *n.s.* non-significant

Table 3 Categories of body height related to tendon length

Height (cm)	Gracilis				Semitendinosus			
	<28 cm	[% (*n*)]	≥28 cm	[% (*n*)]	<28 cm	[% (*n*)]	≥28 cm	[% (*n*)]
≤160 (n = 33)	87.9	(29)	12.1	(4)	81.8	(27)	18.2	(6)
161–165 (n = 47)	78.7	(37)	21.3	(10)	61.7	(29)	38.3	(18)
166–170 (n = 100)	68.0	(68)	32.0	(32)	55.0	(55)	45.0	(45)
171–180 (n = 280)	46.4	(130)	53.6	(150)	30.7	(86)	69.3	(194)
181–190 (n = 213)	23.7	(50)*	76.3	(161)*	13.6	(29)	86.4	(184)
≥191 (n = 42)	16.7	(7)	83.3	(35)	7.1	(3)	92.9	(39)
Total (n = 715)	45.0	(321)*	55.0	(392)*	32.0	(229)	68.0	(486)

n number
* 2 missing values gracilis length

Table 4 Predictors of diameter graft < 8 mm

	Univariate			Multivariate		
	OR	(95 % CI)	*P* value	OR	(95 % CI)	*P* value
Age	0.98	(0.95; 1.01)	n.s.	–	–	–
Gender (female)	4.5	(2.3; 8.7)	<0.001	4.5	(1.9; 11.0)	0.001
Weight	0.95	(0.93; 0.98)	0.001	0.97	(0.93; 1.01)	n.s.
Height	0.96	(0.93; 0.99)	0.019	1.04	(0.99; 1.10)	n.s.

OR odds ratios, *95 % CI* 95 % confidence interval, *n.s.* non-significant

Table 5 Gender related to diameter graft

	<8 mm [% (*n*)]		8 mm [% (*n*)]		>8 mm [% (*n*)]	
Male (*n* = 467)	2.8	(13)	36.8	(172)	60.4	(282)
Female (*n* = 256)	11.3	(29)	73.1	(178)	15.6	(40)
Total (*n* = 723)	5.8	(42)	49.7	(359)	44.5	(322)

Two missing values graft diameter, *n* number

References

1. Barrett GR, Luber K, Replogle WH, Manley JL (2010) Allograft anterior cruciate ligament reconstruction in the young, active patient: Tegner activity level and failure rate. Arthroscopy 26(12):1593–1601

2. Boisvert CB, Aubin ME, DeAngelis N (2011) Relationship between anthropometric measurements and hamstring autograft diameter in anterior cruciate ligament reconstruction. Am J Orthop (Belle Mead NJ) 40(6):293–295

3. Borchers JR, Pedroza A, Kaeding C (2009) Activity level and graft type as risk factors for anterior cruciate ligament graft failure: a case-control study. Am J Sports Med 37(12):2362–2367

4. Celiktas M, Golpinar A, Kose O, Sutoluk Z, Celebi K, Sarpel Y (2013) Prediction of the quadruple hamstring autograft thickness in ACL reconstruction using anthropometric measures. Acta Orthop Traumatol Turc 47(1):14–18

5. Chiang ER, Ma HL, Wang ST, Hung SC, Liu CL, Chen TH (2012) Hamstring graft sizes differ between Chinese and Caucasians. Knee Surg Sports Traumatol Arthrosc 20(5):916–921

6. Claes S, Vereecke E, Maes M, Victor J, Verdonk P, Bellemans J (2013) Anatomy of the anterolateral ligament of the knee. J Anat 223(4):321–328

7. Conte EJ, Hyatt AE, Gatt CJ, Jr., Dhawan A (2014) Hamstring autograft size can be predicted and is a potential risk factor for anterior cruciate ligament reconstruction failure. Arthroscopy 30(7):882–890

8. Cooper MT, Kaeding C (2010) Comparison of the hospital cost of autograft versus allograft soft-tissue anterior cruciate ligament reconstructions. Arthroscopy 26(11):1478–1482

9. Engelman GH, Carry PM, Hitt KG, Polousky JD, Vidal AF (2014) Comparison of allograft versus autograft anterior cruciate ligament reconstruction graft survival in an active adolescent cohort. Am J Sports Med 42(10):2311–2318

10. Filho ES, Sampaio EB, Namba M, Silva JL, Albano M, Rocha LE, Agulham MA, Cunha LA (2010) [Is it possible to predict the length of knee flexor tendons by anthropometry?]. Rev Col Bras Cir 37(4):274–278

11. Golant A, Quach T, Rosen JE (2014) Medial patellofemoral ligament reconstruction with a looped semitendinosus tendon, using knotless anchor fixation on the patella and hybrid fixation on the femur. Arthrosc Tech 3(2):e211–216

12. Janssen RP, van der Velden MJ, Pasmans HL, Sala HA (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21(4):898–905

13. Kaeding CC, Aros B, Pedroza A, Pifel E, Amendola A, Andrish JT, Dunn WR, Marx RG, McCarty EC, Parker RD, Wright RW, Spindler KP (2011) Allograft versus autograft anterior cruciate ligament reconstruction: predictors of failure from a MOON prospective longitudinal cohort. Sports Health 3(1):73–81

14. Kvist J, Kartus J, Karlsson J, Forssblad M (2014) Results from the Swedish national anterior cruciate ligament register. Arthroscopy 30(7):803–810

15. Laprade RF, Wijdicks CA (2012) Surgical technique: development of an anatomic medial knee reconstruction. Clin Orthop Relat Res 470(3):806–814

16. Limitlaohaphan C, Kijkunasatian C, Saitongdee P (2009) Length of semitendinosus and gracilis tendons and the relationship of graft length and leg length. J Med Assoc Thai 92 Suppl 6:S200–203

17. Lubowitz JH (2012) All-inside anterior cruciate ligament graft link: graft preparation technique. Arthrosc Tech 1(2):e165–168

18. Ma CB, Keifa E, Dunn W, Fu FH, Harner CD (2010) Can pre-operative measures predict quadruple hamstring graft diameter? Knee 17(1):81–83

19. Macaulay AA, Perfetti DC, Levine WN (2012) Anterior cruciate ligament graft choices. Sports Health 4(1):63–68

20. Magnussen RA, Lawrence JT, West RL, Toth AP, Taylor DC, Garrett WE (2012) Graft size and patient age are predictors of early revision after anterior cruciate ligament reconstruction with hamstring autograft. Arthroscopy 28(4):526–531

21. Mariscalco MW, Flanigan DC, Mitchell J, Pedroza AD, Jones MH, Andrish JT, Parker RD, Kaeding CC, Magnussen RA (2013) The influence of hamstring autograft size on patient-reported outcomes and risk of revision after anterior cruciate ligament reconstruction: a Multicenter Orthopaedic Outcomes Network (MOON) Cohort Study. Arthroscopy 29(12):1948–1953

22. Middleton KK, Hamilton T, Irrgang JJ, Karlsson J, Harner CD, Fu FH (2014) Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1. Knee Surg Sports Traumatol Arthrosc 22(7):1467–1482

23. Nagda SH, Altobelli GG, Bowdry KA, Brewster CE, Lombardo SJ (2010) Cost analysis of outpatient anterior cruciate ligament reconstruction: autograft versus allograft. Clin Orthop Relat Res 468(5):1418–1422

24. Papastergiou SG, Konstantinidis GA, Natsis K, Papathanasiou E, Koukoulias N, Papadopoulos AG (2012) Adequacy of semitendinosus tendon alone for anterior cruciate ligament reconstruction graft and prediction of hamstring graft size by evaluating simple anthropometric parameters. Anat Res Int 2012:424158

25. Park SY, Oh H, Park S, Lee JH, Lee SH, Yoon KH (2013) Factors predicting hamstring tendon autograft diameters and resulting failure rates after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21(5):1111–1118

26. Pichler W, Tesch NP, Schwantzer G, Fronhofer G, Boldin C, Hausleitner L, Grechenig W (2008) Differences in length and cross-section of semitendinosus and gracilis tendons and their effect on anterior cruciate ligament reconstruction: a cadaver study. J Bone Joint Surg Br 90(4):516–519

27. Pinheiro LF, Jr., de Andrade MA, Teixeira LE, Bicalho LA, Lemos WG, Azeredo SA, da Silva LA, Gonzaga LG (2011) Intra-operative four-stranded hamstring tendon graft diameter evaluation. Knee Surg Sports Traumatol Arthrosc 19(5):811–815

28. Prodromos C, Joyce B, Shi K (2007) A meta-analysis of stability of autografts compared to allografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 15(7):851–856

29. Reboonlap N, Nakornchai C, Charakorn K (2012) Correlation between the length of gracilis and semitendinosus tendon and physical parameters in Thai males. J Med Assoc Thai 95 Suppl 10:S142–146

30. Samuelsson K, Andersson D, Ahlden M, Fu FH, Musahl V, Karlsson J (2013) Trends in surgeon preferences on anterior cruciate ligament reconstructive techniques. Clin Sports Med 32(1):111–126

31. Schwartzberg R, Burkhart B, Lariviere C (2008) Prediction of hamstring tendon autograft diameter and length for anterior cruciate ligament reconstruction. Am J Orthop (Belle Mead NJ) 37(3):157–159

32. Schwartzberg RS (2014) Prediction of semitendinosus and gracilis tendon lengths and diameters for double bundle ACL reconstruction. Am J Orthop (Belle Mead NJ) 43(1):E1–6

33. Singhal MC, Gardiner JR, Johnson DL (2007) Failure of primary anterior cruciate ligament surgery using anterior tibialis allograft. Arthroscopy 23(5):469–475

34. Spencer EA, Appleby PN, Davey GK, Key TJ (2002) Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr 5(4):561–565

35. Thomas S, Bhattacharya R, Saltikov JB, Kramer DJ (2013) Influence of anthropometric features on graft diameter in ACL reconstruction. Arch Orthop Trauma Surg 133(2):215–218

36. Treme G, Diduch DR, Billante MJ, Miller MD, Hart JM (2008) Hamstring graft size prediction: a prospective clinical evaluation. Am J Sports Med 36(11):2204–2209

37. Tuman JM, Diduch DR, Rubino LJ, Baumfeld JA, Nguyen HS, Hart JM (2007) Predictors for hamstring graft diameter in anterior cruciate ligament reconstruction. Am J Sports Med 35(11):1945–1949

38. Xie G, Huangfu X, Zhao J (2012) Prediction of the graft size of 4-stranded semitendinosus tendon and 4-stranded gracilis tendon for anterior cruciate ligament reconstruction: a Chinese Han patient study. Am J Sports Med 40(5):1161–1166

REGENERATION OF HAMSTRING TENDONS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Rob P.A. Janssen, Maria J.F. van der Velden,
Huub L.M. Pasmans, Harm A.G.M. Sala

Knee Surgery, Sports Traumatology, Arthroscopy 2013;21:898–905

Abstract

Purpose
Primary aim of the study was analysis of hamstring tendon regeneration after anterior cruciate ligament (ACL) reconstruction. Secondary aim was analysis of isokinetic muscle strength in relation to hamstring regeneration. The hypothesis was that regeneration of hamstring tendons after ACL reconstruction occurs and that regenerated hamstring tendons contribute to isokinetic hamstring strength with regeneration distal to the knee joint line.

Methods
Twenty-two patients scheduled for ACL reconstruction underwent prospective MRI analysis of both legs. MRI parameters were tendon regeneration and morphology, muscle retraction and muscle cross-sectional area. A double-blind, prospective analysis of isokinetic quadriceps and hamstrings strength was performed.

Results
Regeneration of the gracilis tendon after ACL reconstruction occurred in all patients. Regeneration of the semitendinosus tendon occurred in 14 patients. At 1 year, the surface area of the semitendinosus and gracilis muscle decreased compared to both preoperatively ($P < 0.01$) and the contralateral leg ($P < 0.01$). The cross-sectional area of the semitendinosus muscle decreased in the absence of tendon regeneration ($P = 0.05$). The cross-sectional area of the gracilis muscle was greater in case of regeneration distal to the joint line ($P = 0.01$). Muscle retraction of the semitendinosus muscle was increased in case of nonregeneration ($P = 0.02$). There was no significant relationship between isokinetic flexion strength and tendon regeneration.

Conclusion
Hamstring tendons regenerated after harvest of both semitendinosus and gracilis tendons for ACL reconstruction. There was no relation between isokinetic flexion strength and tendon regeneration.

Keywords
Anterior cruciate ligament reconstruction · Hamstring · Semitendinosus · Gracilis · Regeneration · MRI

Level of evidence II

Introduction

Hamstring tendons are frequently used as autograft for single- and double-bundle anterior cruciate ligament (ACL) reconstruction. Regeneration of hamstring tendons, to various extends, has previously been reported.[4–7, 14, 16, 20, 21, 23, 27]

In 1982, Lipscomb et al.[12] reported results of hamstring muscle strength after ACL reconstruction using autograft hamstring tendons. Regeneration of hamstring tendons after ACL reconstruction was first described by Cross et al. in 1992.[4] Part of their study was analysis of upper leg flexion and extension muscle strength in analogy of the work by Lipscomb et al.[12] In addition to hamstring regeneration and muscle strength after ACL reconstruction, Simonian et al.[21] examined the cross-sectional area of individual hamstring muscles as well as the insertion site of the regenerated tendons. Later, mostly retrospective research on regeneration of hamstring tendons after ACL reconstruction focused on muscle cross-sectional area[5, 7, 20, 23, 27], retraction of hamstring muscle[7, 14, 27] and muscle strength.[7, 14, 22, 23]

A prospective MRI study, comparing patients with and without tendon regeneration in regard to isokinetic muscle strength, has only been performed by Eriksson et al.[7] They used a single hamstring tendon (semitendinosus) for ACL reconstruction. To our knowledge, no such study has been performed after harvest of both semitendinosus and gracilis tendons for ACL reconstruction.

The primary purpose of the present study was to demonstrate regeneration and morphology of semitendinosus and gracilis tendons after ACL reconstruction using both hamstring tendons. In addition, isokinetic flexion and extension strength were examined between patients with and without hamstring tendon regeneration.
The hypothesis was that both semitendinosus and gracilis tendons regenerate after harvest for ACL reconstruction. Furthermore, we hypothesized that isokinetic muscle strength is better restored in case of regeneration of hamstring tendons distal to the joint line.

Materials and methods

Inclusion criteria were the following: chronic unilateral ACL-deficient knee without any concomitant knee ligament injury and informed consent to participate in the study.

Exclusion criteria were the following: (1) fractures of either lower extremity in the past; (2) previous ACL, hamstring or quadriceps surgery; (3) contra-indications for MRI.

The study consisted of 2 parts. The first part was a prospective MRI study to determine the regeneration of semitendinosus and gracilis tendons after ACL reconstruction. Consecutive patients, who fulfilled the entry criteria as defined by the study protocol, underwent MRI of both legs preoperatively as well as 2 weeks, 6 and 12 months postoperatively.

All patients were operated by the same orthopaedic surgeon (HS). ACL reconstruction was performed using a 4-strand hamstring autograft (semitendinosus and gracilis). All patients were rehabilitated according to a standardized accelerated brace-free rehabilitation protocol.

The second part was a prospective, double-blind study of isokinetic strength of quadriceps and hamstring muscles of both legs. Patients were examined preoperatively and 6 and 12 months postoperatively. Patients were evaluated by Tegner-, Lysholm- and International Knee Documentation Committee (IKDC) scores. Upper leg circumference measurements and KT-1000 laxity testing at 89 and 133 Newton (MEDmetric Co., San Diego, CA, USA) of both legs were performed. An isokinetic strength protocol was used to test quadriceps and hamstring muscles. All patients were examined by the same independent examiner (RJ). Patients and examiner were blinded for the MRI results.

In order to compare the results between patients with and without hamstring tendon regeneration, patients were classified in one of the following 3 groups: no hamstring regeneration, regeneration of one tendon or regeneration of 2 tendons. The last 2 groups (with hamstring regeneration) were further classified in either proximal or distal reattachment of the tendon, in reference to the knee joint line.

The semitendinosus and gracilis muscles have also been divided in separate groups with or without tendon regeneration. In case of tendon regeneration, further subdivision was made in either proximal or distal reattachment of the tendon (in reference to the knee joint line).

Written informed consent was documented in all patients. They participated voluntarily in the study and did not receive a reward of any kind. The study was approved by an independent medical ethics committee (METC-number 0110; Máxima Medical Centre, Veldhoven, The Netherlands).

Surgical Procedure
One orthopaedic surgeon (HS) performed ACL reconstructions in all 22 patients. A 4 to 5 cm vertical skin incision was made over the pes anserinus. The crural fascia (layer 1 according to Warren and Marshall[26]) was incised in a longitudinal fashion, proximal to the hamstring tendons extending distally over the pes anserinus. A closed tendon stripper was used to remove the gracilis and semitendinosus tendons. Arthroscopic ACL reconstruction was performed with Bone Mulch screw femoral fixation and WasherLoc tibial fixation (Arthrotek, Warsaw, In, USA). The crural fascia was not sutured. The standardized rehabilitation protocol has been described in a previous publication.[10]

MRI
Preoperatively, MRI scans of both legs were made simultaneously by a standardized protocol with a 1.5 Tesla MRI (Philips Medical Systems, Best, The Netherlands). The MRI of both legs was repeated postoperatively at 14 (~14.3 ± 1.9) days, 6 (~6.2 ± 0.9) months and 12 (~12.4 ± 1.6) months. Both knees were positioned in a body coil in full extension and 15 degrees exorotation. T1 and T2 weighted transaxial images were made starting 1 cm distal to the tibial tuberosity till 30 cm proximal to the knee joint line. Repetition time (TR) was 489 ms and 2770 ms, and echo time (TE) was 10 ms and 100 ms for the T1 and T2 weighted images respectively. Matrix size 512 x 512 pixels, field of view (FOV) 360 x 360 mm. The slice thickness was 8.0 mm and slice intersection gap 1.0 mm. Sagittal images were also made extending from 8 cm distal to the knee joint line up to 32 cm proximal to the knee joint line. These images were made with TR 500 ms, TE 10 ms, matrix size 512 x 512 pixels, FOV 400 x 400 mm, slice thickness 4.0 mm and slice intersection gap of 0.4 mm.

Measurements were made of the following muscles: semitendinosus, gracilis, semimembranosus and long head of the biceps femoris. On the preoperative scans, the maximal cross-sectional area of all four muscles was measured.

The exact distance in the sagittal plane, between the joint line and the maximal cross-sectional area was recorded per patient and per muscle. This same distance was used on the postoperative scans of the patient to compare the cross-sectional areas of the four muscles.

The following additional MRI parameters were determined: (1) distance between the joint line and preoperative distal muscle-tendon junction of semitendinosus and gracilis; (2) distance between the joint line and the distal muscle ends of semitendinosus and gracilis after tendon harvesting; (3) distance between the joint line and distal muscle-tendon junction in case of tendon regeneration; (4) distance between the joint line and distal muscle end in case of no tendon regeneration; (5) anatomic insertion site of regenerated tendon.

The MRI scans were examined by two independent examiners (HP, MV) with measurements made on both legs.

Isokinetic testing protocol
All patients underwent isokinetic strength tests of quadriceps and hamstrings of both legs preoperatively. A standardised test protocol was performed using the Biodex System III dynamometer (Biodex Medical Systems, Shirley, NY, USA). The test protocol was repeated at 6 (~6.6 ± 1.0) months and 12 (~13.0 ± 2.0) months postoperatively. All tests were performed by an independent examiner (RJ). Both examiner and patients were blinded for the MRI results. After a 10-minute warm-up period on a cycle ergometer (50 W), isokinetic testing was performed in sitting position with hip flexed 60 degrees. The upper body, pelvis and thigh of the tested upper leg were stabilized with straps. The lower leg fixation was at 20 cm distal to the knee joint line, to minimize the effect of knee joint instability on muscle strength performance. A concentric-concentric knee test protocol, with gravitational correction, was performed allowing full range of flexion and extension at 60, 180 and 300 °/sec. The patient was instructed to maximally extend the knee (up to the level of the examiners hand) as well as maximal flexion. The test consisted of 5 maximal torques for quadriceps and hamstrings strength at 60, 180 and 300 °/sec with a 10-s pause between the 3 angle velocities. During 1-min rest, the dynamometer was installed for the contralateral leg and the same test sequence performed. Peak values in Newton meters and total work in Joules (area under the curve) was calculated in each test. The reliability of the test was determined by the variation coefficient and curve pattern. Comparisons between both legs were made as well as comparison in time for each leg separately.

Statistical analysis
Statistical analysis was performed using SPSS 19.0. A sample size calculation was performed for the study. The primary endpoint was the difference in cross-sectional area preoperatively compared to postoperatively. With a difference of 2 in the mean response and a standard deviation of 3, 20 pairs of subjects were needed. The used alpha associated with this paired test was 0.05, and the power was 0.8. Twenty-two patients were included in the study. The results displayed few normal distributions. For this reason, median instead of average values were used. The Wilcoxon signed rank test was used to determine pre- and postoperative differences as well as the differences between both legs. Differences among patients with and without hamstring regeneration were assessed by the Mann-Whitney U test. Significance was set at ≤ 0.05.

Results

Twenty-two consecutive patients, who fulfilled the entry criteria as defined by the study protocol, were included in the study. There were 17 men and 5 women with a mean age of 28.4 years ± 5.0 (21-37).

MRI
A total of 5 out of 88 MRI scans were missing upon review: one preoperative scan, one 2-weeks postoperative scan, one 6-months postoperative scan, and two 12-months postoperative scans. As a consequence, it was not possible to analyse the results of muscle retraction and cross-sectional area in three patients when comparing preoperative and 12-months postoperative results. However, the hamstring tendon regeneration could be evaluated in all patients using either the 6- or 12-months postoperative MRI-scan.

The results of hamstring regeneration are presented in Fig. 1. All 22 patients demonstrated hamstring regeneration after harvest for ACL reconstruction. Figures 2 and 3 show the specific results of semitendinosus and gracilis regeneration, respectively.
Figures 4 and 5 demonstrate a series of MRI proximal and distal to the joint line in a patient with regeneration of both semitendinosus and gracilis tendons.

Results of cross-sectional area of semitendinosus and gracilis muscles are presented in Tables 1-4. All gracilis tendons regenerated. For that reason, the gracilis muscle cross-sectional area in the group of patients with tendon regeneration proximal to the joint line was compared to the group of patients with gracilis regeneration distal to the joint line (Table 4).

Table 5 demonstrates the amount of retraction of semitendinosus muscles. There was no significant compensatory hypertrophy of the semimembranosus and biceps femoris muscles after hamstring tendon harvest.

Clinical outcome and isokinetic strength
Sixteen of the 22 patients have been evaluated at clinical and isokinetic follow-up at 12 months postoperatively. The remaining group of 6 patients was evaluated at 6 months postoperatively only. They did not return for follow-up at 12 months. The rehabilitation was not considered complete at 6 months postsurgery; therefore these 6 patients were not included in the final review of clinical outcome and isokinetic strength analysis. The clinical outcomes are presented in Table 6.

No significant differences were found when comparing pre- and postoperative isokinetic extension and flexion strength in terms of: (1) peak torque and total work between the operated and contralateral leg; (2) percentage increase or decrease of peak torque and total work between the operated and contralateral leg. No significant differences were found in flexion and extension strength (peak torque and total work) between the group of patients with regeneration of both hamstring tendons distal to the joint line, and the group of patients with only 1 regenerated tendon proximal to the joint line.

Discussion

The most important finding of the present study was that hamstring tendons regenerated after ACL reconstruction. There was no relation between isokinetic flexion strength and tendon regeneration.

Regeneration of all gracilis tendons after ACL reconstruction, with harvest of both gracilis and semitendinosus tendon, was found in MRI studies by Simonian et al.[21] and Williams et al.[27] Williams et al. found 63% of the regenerated gracilis tendons to insert distal to the joint line, Simonian et al. 33%. Regeneration of the semitendinosus tendon occurred in 7 out of 8 patients (88%) in the study by Williams et al.[27] They described that 25% attached distal to the joint line.[27] Simonian et al.[21] described semitendinosus tendon regeneration in 6 out of 9 patients (66%); all 6 tendons inserted on the tibia. These results are similar to the results of the present study.

In contrast, Takeda et al.[23] described a group of 11 patients with semitendinosus regeneration in all cases. In 10 patients (91%), the semitendinosus tendon inserted distal to the joint line. The gracilis tendon regenerated in 9 of their patients (82%), but none inserted on the tibia.[23] Tadokoro et al.[22] examined a larger group of 28 patients. They described 79% semitendinosus tendon regeneration with only 46% gracilis tendon regeneration. The authors did not specify the level of insertion.[22] In their MRI follow-up study following hamstring harvest for ACL reconstruction, Rispoli et al. did not make a distinction between semitendinosus and gracilis tendon regeneration.[20]

Various theories exist to explain the phenomenon of regeneration of hamstring tendons after harvest for ACL reconstruction. Some authors postulated regeneration to start at the distal end of semitendinosus and gracilis muscle for reason of increased vascularity.[4, 20] The tendon then regenerates in a distal fashion. Cross et al.[4] and Rispoli et al.[20] viewed the anatomic space between medial layer 1 and 2[26] as a tubular pathway for the regenerating tendons. This is in analogy of repair of nerve lesions along intact epineural tissue.[4, 20]

Tadokoro et al.[22] hypothesized that the gracilis tendon is surrounded by less fascial layers than the semitendinosus tendon. They reported this as a possible explanation for their results of less gracilis tendon regenerations compared to semitendinosus tendon regenerations.[22] This theory of regeneration is not supported by the work by Simonian et al.[21], Williams et al.[27], as well as the present study where gracilis tendon regeneration occurred more frequently than semitendinosus tendon regeneration. Carofino et al.[3] also opposed to this theory. In contrast to the view of Cross et al.[4] and Rispoli et al.[20], Carofino et al. described the pathway between medial layer 1 and 2 as not being tubular in shape. For this reason, they concluded that these fascial layers cannot lead to the similar shape of the regenerated tendons compared to their original morphology.[3]

Other authors postulated a second theory to explain hamstring regeneration after harvest for ACL reconstruction. In the void space following harvest, a haematoma is formed. Fibroblast precursor cells migrate from surrounding tissues into this haematoma. They start fibroblast proliferation and collagen production. Limited mechanical stress leads to organisation of collagen fibres and possible maturation into a regenerated hamstring tendon.[6, 19]

Histological studies of regenerated tendons have found very similar tissue compared to the original hamstring tendons.[8, 18] At 1-year follow-up, the regenerated tendon showed longitudinal, well organized collagen with fibroblast-like nuclei. However, the total distribution of collagen fibres and cell nuclei was more irregular in comparison to the original tendon tissue.[18] At 2-year follow-up, the central zone of the regenerated tendon demonstrated collagen fibre bundles surrounded by fibrous tissue with fibroblast proliferation.[8]

Previous studies on hamstring tendon regeneration, in relation to morphology and/or muscle strength, did not distinguish between patients with or without tendon regeneration.[4, 17, 20-23, 27] In the present study, an analysis was made of muscle retraction, cross-sectional area and isokinetic flexion strength comparing patients with or without tendon regeneration. All patients showed a significant decrease in muscle cross-sectional area after 12 months for both semitendinosus and gracilis muscle, in comparison to preoperative and contralateral values. Similar results were found by other authors.[7, 9, 13, 17, 27]

Williams et al. reported a significant decrease in muscle cross-sectional area as well as muscle volume of both semitendinosus and gracilis muscles at 6 months postsurgery in comparison to the preoperative and contralateral values.[27] At 12-16 months postsurgery, Irie et al. found a decrease in muscle cross-sectional area of 47.1% for semitendinosus and 51.1% for gracilis muscles compared to the contralateral leg.[9] Eriksson et al.[7], Makihara et al.[13] and Nishino et al.[17] found a significant decrease in semitendinosus cross-sectional area compared to the contralateral leg. In their cases, only the semitendinosus tendon was harvested for ACL reconstruction.

In contrast, Rispoli et al.[20] and Takeda et al.[23] reported no significant decrease in semitendinosus cross-sectional area after ACL reconstruction using both semitendinosus and gracilis tendons.

However, regarding the gracilis muscle cross-sectional area, Takeda et al. did report a significant decrease in cross-sectional area.[23]

In the present study, a significant decrease in cross-sectional area for both semitendinosus and gracilis was demonstrated regardless of tendon regeneration. In addition, the cross-sectional area of both semitendinosus and gracilis muscles was significantly smaller in case of regeneration of only one tendon proximal to the joint line compared to regeneration of both tendons distal to the joint line. This would suggest that tendon regeneration, distal to the joint line, leads to a more functional muscle condition. Eriksson et al.[5] found similar significant results. In contrast to the present study, they only harvested the semitendinosus tendon for ACL reconstruction.

Hypothetically, the amount of compensatory hypertrophy of semimembranosus and biceps femoris muscles may be related to the number of harvested hamstring tendons for ACL reconstruction. Eriksson et al.[7] demonstrated this phenomenon in patients without regeneration of the harvested semitendinosus tendon. In contrast, the present study did not show significant compensatory hypertrophy of semimembranosus nor biceps femoris muscles after harvest of both gracilis and semitendinosus tendons for ACL reconstruction. These results are similar to the findings by Simonian et al.[21] and Takeda et al.[23]

Nakamae et al.[14], Nishino et al.[17] and Williams et al.[27] found significant muscle retraction of both hamstring tendons after ACL reconstruction. Similar results were found in the present study. If a tendon does not regenerate after harvest, the muscle appears to be nonfunctional as demonstrated by the progressive muscle retraction up to 1 year postsurgery.

No relation was found in the present study between regeneration of hamstring tendons after ACL reconstruction and isokinetic flexion and extension muscle strength. Eriksson et al.[7] and Tadokoro et al.[22] similarly found no significant difference in muscle strength between patients with and without tendon regeneration. Kim et al.[11] performed a comparative study between hamstring-harvested and hamstring-unharvested patients after ACL reconstruction. They showed a significant knee flexion weakness in the operated leg compared to the contralateral side, regardless of hamstring harvesting.[11]

There are some limitations to the present study. The isokinetic strength testing did not include deep flexion and internal rotation of the tibia. Various studies have demonstrated that these two factors may be significantly decreased after ACL reconstruction with hamstring tendons.[1, 2, 9, 13, 15, 22, 24, 25] It cannot be ruled out that these specific muscle strengths could have shown a significant decrease in patients without tendon regeneration in the present study.
The second limitation to the present study is the absent follow-up of 6 patients for isokinetic testing at 12 months postoperatively. This has reduced the number of patients to 16 (out of 22) in the isokinetic strength analysis.

The clinical relevance of the present study is that patients may be informed that hamstring tendons regenerate after retrieval for ACL reconstruction. It also indicates that hamstring autograft ACL reconstruction may be associated with less morbidity than previously thought. This might influence future rehabilitation protocols.

Conclusion

Hamstring tendons regenerated after harvest of both semitendinosus and gracilis tendons for ACL reconstruction. There was no correlation between isokinetic flexion strength and tendon regeneration.

Acknowledgment
We would like to thank Saskia Houterman PhD, epidemiologist for her assistance in the statistical analysis of the study.

Fig. 1 Regeneration of hamstring tendons and the insertion level

(*ST* semitendinosus tendon; *G* gracilis tendon; *neo-tendon* regenerated tendon; *prox.* proximal; *jl* joint line)

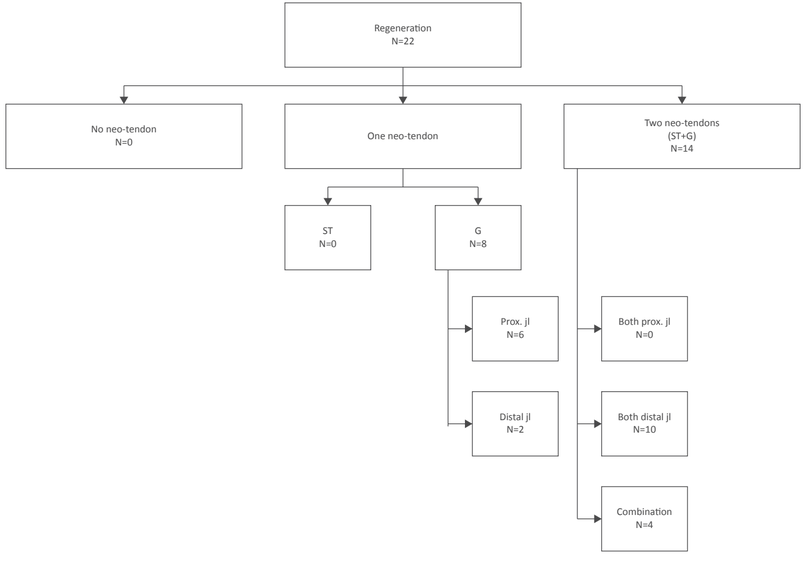


Fig. 2 Regeneration of semitendinosus tendon (ST) and the insertion level

(*ST* semitendinosus tendon; *G* gracilis tendon; *neo-tendon* regenerated tendon; *prox.* proximal; *jl* joint line)

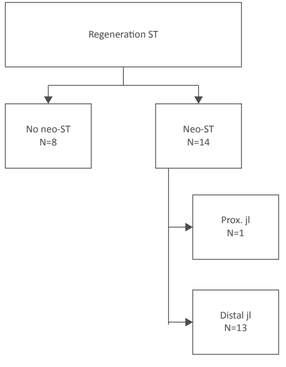


Fig. 3 Regeneration of gracilis tendon (G) and the insertion level

(*neo-G* regenerated gracilis tendon; *prox.* proximal; *jl* joint line)

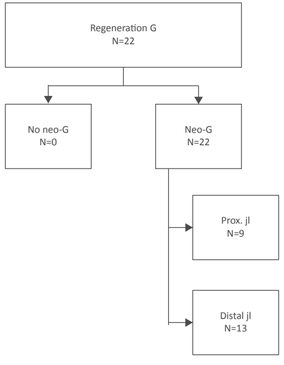
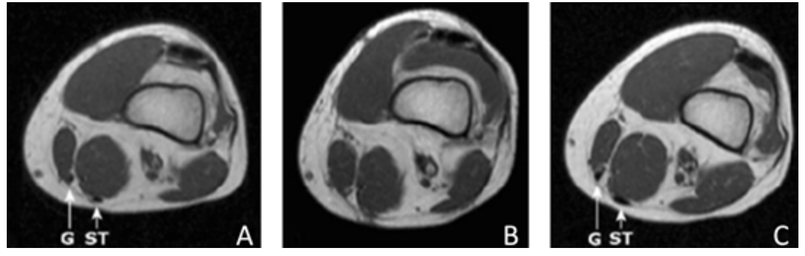
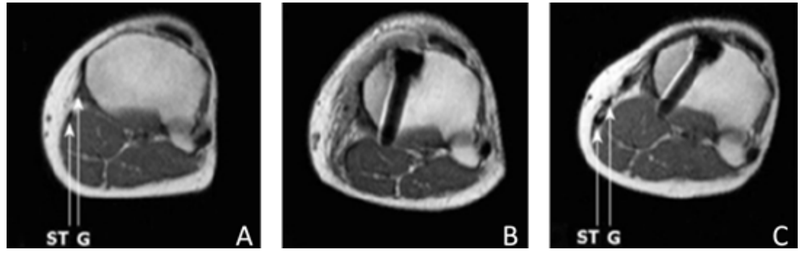


Fig. 4



Transverse MRI images of gracilis (G) and semitendinosus (ST) tendons of same patient 6.3 cm proximal to the joint line at time intervals: **a** preoperative; **b** 2 weeks postoperatively; **c** 12 months postoperatively

Fig. 5



Transverse MRI images of gracilis (G) and semitendinosus (ST) tendons of same patient 2.7 cm distal to the joint line at time intervals: **a** preoperative; **b** 2 weeks postoperatively; **c** 12 months postoperatively

Table 1

Cross-sectional area (cm^2) of the semitendinosus and gracilis muscles preoperatively and at 12 months postoperatively

	Preoperative	12 months postoperatively	*P* value
Semitendinosus	12.2 (±3.3)	8.3 (±3.0)	<0.01
Gracilis	4.9 (±1.2)	3.6 (±1.2)	<0.01

Table 2

Cross-sectional area (cm^2) of the semitendinosus and gracilis muscles comparing the operated versus the contralateral leg at 12 months postoperatively

	Operated leg	Contralateral leg	*P* value
Semitendinosus	8.3 (±3.0)	14.0 (±4,1)	<0.01
Gracilis	3.6 (±1.2)	5.1 (±1.4)	<0.01

Table 3

Cross-sectional area (cm^2) of the semitendinosus muscles without tendon regeneration and regeneration distal to the joint line at 12 months postoperatively (*neo-tendon* regenerated tendon)

	No neo-tendon	Neo-tendon distal to joint line	*P* value
Semitendinosus	6.0 (±2.1)	10.0 (±2.6)	0.05

Table 4

Cross-sectional area (cm^2) of the gracilis muscles with tendon regeneration proximal and distal to the joint line at 12 months postoperatively (*neo-tendon* regenerated tendon)

	Neo-tendon proximal to joint line	Neo-tendon distal to joint line	*P* value
Gracilis	2.8 (±0.7)	4.8 (±1.1)	0.01

Table 5

Semitendinosus muscle retraction (cm) without tendon regeneration and regeneration distal to the joint line at 12 months postoperatively (*neo-tendon* regenerated tendon)

	No neo-tendon	Neo-tendon distal to joint line	*P* value
Semitendinosus	13.0 (±3.4)	3.8 (±2.0)	0.02

Table 6

Clinical outcomes

	Preoperative	12-months postoperatively	*P* value
IKDC			
A	0 (0 %)	2 (13 %)	
B	0 (0 %)	10 (62 %)	
C	4 (18 %)	3 (19 %)	
D	18 (82 %)	1 (6 %)	
Tegner	4 (3-5)	7 (4-9)	<0.01
Lysholm	70 (±10) points	93 (±10) points	<0.01
KT-1000 side to side difference			
89 N	5 (±3) mm	2 (±4) mm	<0.01
133 N	7 (±3) mm	2 (±3) mm	<0.01
Upper leg circumference			
Operated leg	40 (±3) cm	39 (±3) cm	0.05
Contralateral leg	40 (±2) cm	40 (±2) cm	

References

1. Ardern CL, Webster KE, Taylor NF, Feller JA (2010) Hamstring strength recovery after hamstring tendon harvest for anterior cruciate ligament reconstruction: a comparison between graft types. Arthroscopy 26(4):462–469

2. Armour T, Forwell L, Litchfield R, Kirkley A, Amendola N, Fowler PJ (2004) Isokinetic evaluation of internal/external tibial rotation strength after the use of hamstring tendons for anterior cruciate ligament reconstruction.
Am J Sports Med 32(7):1639–1643

3. Carofino B, Fulkerson J (2005) Medial hamstring tendon regeneration following harvest for anterior cruciate ligament reconstruction: fact, myth, and clinical implication. Arthroscopy 21(10):1257–1265

4. Cross MJ, Roger G, Kujawa P, Anderson IF (1992) Regeneration of the semitendinosus and gracilis tendons following their transection for repair of the anterior cruciate ligament. Am J Sports Med 20(2):221–223

5. Eriksson K, Larsson H, Wredmark T, Hamberg P (1999) Semitendinosus tendon regeneration after harvesting for ACL reconstruction. A prospective MRI study.
Knee Surg Sports Traumatol Arthrosc 7(4):220–225

6. Eriksson K, Kindblom LG, Hamberg P, Larsson H, Wredmark T (2001) The semitendinosus tendon regenerates after resection: a morphologic and MRI analysis in 6 patients after resection for anterior cruciate ligament reconstruction.
Acta Orthop Scand 72(4):379–384

7. Eriksson K, Hamberg P, Jansson E, Larsson H, Shalabi A, Wredmark T (2001) Semitendinosus muscle in anterior cruciate ligament surgery: Morphology and function. Arthroscopy 17(8):808–817

8. Ferretti A, Conteduca F, Morelli F, Masi V (2002) Regeneration of the semitendinosus tendon after its use in anterior cruciate ligament reconstruction: a histologic study of three cases. Am J Sports Med 30(2):204–207

9. Irie K, Tomatsu T (2002) Atrophy of semitendinosus and gracilis and flexor mechanism function after hamstring tendon harvest for anterior cruciate ligament reconstruction. Orthopedics 25(5):491–495

10. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299–1306

11. Kim JG, Yang SJ, Lee YS, Shim JC, Ra HJ, Choi JY (2011) The effects of hamstring harvesting on outcomes in anterior cruciate ligament–reconstructed patients: a comparative study between hamstring–harvested and –unharvested patients.
Arthroscopy 27(9):1226–1234

12. Lipscomb AB, Johnston RK, Snyder RB, Warburton MJ, Gilbert PP (1982) Evaluation of hamstring strength following use of semitendinosus and gracilis tendons to reconstruct the anterior cruciate ligament. Am J Sports Med 10(6):340–342

13. Makihara Y, Nishino A, Fukubayashi T, Kanamori A (2006) Decrease of knee flexion torque in patients with ACL reconstruction: combined analysis of the architecture and function of the knee flexor muscles.
Knee Surg Sports Traumatol Arthrosc 14(4):310–317

14. Nakamae A, Deie M, Yasumoto M, Adachi N, Kobayashi K, Yasunaga Y, Ochi M (2005) Three–dimensional computed tomography imaging evidence of regeneration of the semitendinosus tendon harvested for anterior cruciate ligament reconstruction: a comparison with hamstring muscle strength. J Comput Assist Tomogr 29(2): 241–245

15. Nakamura N, Horibe S, Sasaki S, Kitaguchi T, Tagami M, Mitsuoka T, Toritsuka Y, Hamada M, Shino K (2002) Evaluation of active knee flexion and hamstring strength after anterior cruciate ligament reconstruction using hamstring tendons.
Arthroscopy 18(6):598–602

16. Nikolaou VS, Efstathopoulos N, Wredmark T (2007) Hamstring tendons regeneration after ACL reconstruction: an overview. Knee Surg Sports Traumatol Arthrosc 15(2):153–160

17. Nishino A, Sanada A, Kanehisa H, Fukubayashi T (2006) Knee–flexion torque and morphology of the semitendinosus after ACL reconstruction.
Med Sci Sports Exerc 38(11):1895–1900

18. Okahashi K, Sugimoto K, Iwai M, Oshima M, Samma M, Fujisawa Y, Takakura Y (2006) Regeneration of the hamstring tendons after harvesting for arthroscopic anterior cruciate ligament reconstruction: a histological study in 11 patients.
Knee Surg Sports Traumatol Arthrosc 14(6):542–545

19. Otoshi K, Kikuchi S, Ohi G, Numazaki H, Sekiguchi M, Konno S (2011) The process of tendon regeneration in an achilles tendon resection rat model as a model for hamstring regeneration after harvesting for anterior cruciate ligament reconstruction.
Arthroscopy 27(2):218–227

20. Rispoli DM, Sanders TG, Miller MD, Morrison WB (2001) Magnetic resonance imaging at different time periods following hamstring harvest for anterior cruciate ligament reconstruction. Arthroscopy 17(1):2–8

21. Simonian PT, Harrison SD, Cooley VJ, Escabedo EM, Deneka DA, Larson RV (1997) Assessment of morbidity of semitendinosus and gracilis tendon harvest for ACL reconstruction. Am J Knee Surg 10(2):54–59

22. Tadokoro K, Matsui N, Yagi M, Kuroda R, Kurosaka M, Yoshiya S (2004) Evaluation of hamstring strength and tendon regrowth after harvesting for anterior cruciate ligament reconstruction. Am J Sports Med 32(7):1644–1650

23. Takeda Y, Kashiwaguchi S, Matsuura T, Higashida T, Minato A (2006) Hamstring muscle function after tendon harvest for anterior cruciate ligament reconstruction: evaluation with T2 relaxation time of magnetic resonance imaging.
Am J Sports Med 34(2):281–288

24. Tashiro T, Kurosawa H, Kawakami A, Hikita A, Fukui N (2003) Influence of medial hamstring tendon harvest on knee flexor strength after anterior cruciate ligament reconstruction. A detailed evaluation with comparison of single– and double–tendon harvest. Am J Sports Med 31(4):522–529

25. Viola RW, Sterett WI, Newfield D, Steadman JR, Torry MR (2000) Internal and external tibial rotation strength after anterior cruciate ligament reconstruction using ipsilateral semitendinosus and gracilis tendon autografts. Am J Sports Med 28(4):552–555

26. Warren LF, Marshall JL (1979) The supporting structures and layers on the medial side of the knee: an anatomical analysis. J Bone Joint Surg Am 61(1):56–62

27. Williams GN, Snyder–Mackler L, Barrance PJ, Axe MJ, Buchanan TS (2004) Muscle and tendon morphology after reconstruction of the anterior cruciate ligament with autologous semitendinosus–gracilis graft. J Bone Joint Surg Am 86–A(9):1936–1946

REMODELLING OF HUMAN HAMSTRING AUTOGRAFTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Rob P.A. Janssen, Jasper van der Wijk, Anja Fiedler, Tanja Schmidt, Harm A.G.M. Sala, Sven U. Scheffler

Knee Surgery, Sports Traumatology, Arthroscopy 2011;19:1299–1306

5

Abstract

Purpose
Histological analysis of the remodelling process of human hamstring tendon (HT) grafts after standardized anterior cruciate ligament (ACL) reconstruction with an accelerated rehabilitation protocol.

Methods
Sixty-seven patients underwent retrieval of mid-substance biopsies after clinically successful hamstring autograft ACL reconstruction. Samples were allocated to one of three groups depending on the time point of retrieval: group 1 (6–12 months; n = 15), group 2 (13–24 months; n = 16), group 3 (> 24 months; n = 11). Biopsies from native HT (n = 17) and ACL (n = 8) served as controls. Cellular density, vascular density and myofibroblast density and collagen fibril alignment were analysed by hematoxylin–eosin, Masson–Goldner–Trichrom and immunohistochemical staining protocols.

Results
Compared to native HT (330.4/mm²), total cell number was increased in groups 1–3 (Group 1 = 482.0/mm² (P = 0.036); Group 2 = 850.9/mm² (P = 0.005); and Group 3 = 595.6/mm² (P = 0.043). There were no significant differences between the groups for vessel density. Myofibroblast density was higher in group 2 (199.6/mm²) compared with native HT (1.9/mm², P = 0.014). Collagen orientation was irregular up to 12 months. Thereafter, collagen orientation became more regular, adapting to, but not fully restoring the appearance of the intact ACL. The first 12 months, cells were predominantly ovoid. Ensuing cell morphology changed to spindle-shaped in group 2 and predominantly narrow long cells over 24 months.

Conclusion
Human hamstring grafts showed typical stages of graft remodelling which was not complete up to 2 years after ACL reconstruction. The remodelling process in humans was prolonged compared to the results obtained in several animal studies.

Keywords
Remodelling · Human · Hamstring autograft · Anterior cruciate ligament reconstruction · Myofibroblast

Level of evidence III

Introduction

Anterior cruciate ligament (ACL) ruptures are a common injury in orthopaedic practice. The ACL is frequently replaced by a tendon autograft or allograft to restore normal knee laxity and to prevent development of early osteoarthritis induced by persistent abnormal laxity.[2] Reconstruction techniques were improved over the last 10 years but graft failure is not uncommon: 0.7-10%.[12]

Even though substantial research efforts have been presented on various aspects of ACL reconstruction, little is known about the remodelling process of human ACL grafts.[2, 3, 10, 13, 15, 27, 28, 32-34] Current studies evaluating human biopsies pose inherent limits: often sample size was small and only a limited number of time points were evaluated postoperatively.[6, 11, 18-20, 35] Furthermore, use of different types of grafts limits comparability.[6, 11]

Studies in humans describe a prolonged remodelling process compared with animal studies.[6, 11, 18-20, 35] Most animal studies found completion of the remodelling process between 24 weeks and 1 year. The graft undergoes a transition from its initial biological and biomechanical properties to properties resembling the intact ACL. However, a complete restoration of intact ACL properties has not been found, but an adaptation, which has been termed the ligamentization process.[1, 4, 7, 9, 14, 17, 20, 22, 23, 25, 31]
Knowledge about the duration and the remodelling process itself in humans can potentially influence and improve outcome and rehabilitation protocols following ACL reconstruction.[11, 20]

Aim of this study is to analyse the remodelling process of human hamstring tendon grafts after standardized ACL reconstruction with accelerated brace-free rehabilitation. The hypothesis of the study is that hamstring tendon grafts undergo a remodelling process that will adapt its histological appearance to the morphology of the intact ACL and that this process is completed by one year.

Materials and methods

Sixty-seven patients underwent retrieval of biopsies between 6 and 117 months after replacement of the ACL from 2001 up to 2007. The biopsies were carried out during second-look arthroscopies, which were not associated with the initial ACL reconstruction.

Inclusion criteria were: 1. Previous ACL reconstruction by one senior orthopaedic surgeon (HS) using a 4-strand hamstring autograft with Bone Mulch Screw fixation in femur and WasherLoc fixation on tibia (Arthrotec, Warsaw, IN, USA); 2. No signs of abnormal laxity on clinical examination or at examination under anaesthesia at the time of second-look arthroscopy. A knee with normal laxity is defined as a knee without giving way sensation, KT 1000 < 3 mm differences on 133 N side-to-side testing (MEDmetric Co., San Diego, CA, USA) and a negative pivot shift test; 3. Informed consent to participate in the study.

Exclusion criteria were: 1. Unwillingness to participate in the study; 2. Previous ACL reconstruction by another orthopaedic surgeon or different method of fixation; 3. Abnormal laxity on clinical examination or found in examination under anaesthesia at time of second-look arthroscopy. Abnormal laxity is defined as a knee with giving way sensation, KT-1000 > 3 mm differences on 133 N side-to-side testing and/or positive pivot shift test; 4. Cyclops lesion, extension deficit or other reasons related to possible ACL graft problems; 5. Inadequate tissue sample for histological analysis. The study was approved by the medical ethics board of the Máxima Medical Centre Eindhoven-Veldhoven, The Netherlands. Written informed consent was documented in all patients.

The ACL reconstructions were performed by the same senior orthopaedic surgeon (HS). The surgical technique for ACL reconstruction was identical in all patients: a transtibial technique with Bone Mulch Screw fixation on the femur and WasherLoc fixation on the tibia (surgical technique by S.M. Howell, MD; Fixation materials by Arthrotec, Warsaw, IN, USA). The graft was a double-strand semitendinosus and double-strand gracilis tendon. Tension on the hamstring autograft at time of fixation was 90-100 N, with the knee in full extension.

A standardized accelerated rehabilitation protocol started on the first day postsurgery. Patients were allowed full weight-bearing as tolerated. Crutches were used for the first 2 weeks. In addition to active flexion and extension exercises, the knee was flexed to 90 degrees by means of continuous passive motion machine (OrthoRehab, Oakville, Ontario, Canada). Closed chain exercises were prescribed on the first day postsurgery. Full range of motion was allowed. After discharge, physiotherapy was continued 2-3 times a week according to a standardized brace-free protocol. Unrestricted closed- and open-chain knee-extension exercises were allowed. Resumption of running in a straight line was allowed at 8-10 weeks. Unrestricted return to heavy work activities was allowed after 3 months and competitive contact sports after 4-6 months.

Histological Examination
A single tissue sample was collected from one of the 4 strands of the quadruple hamstring autograft. The synovial layer was cleared from the middle section of the graft bundle. A Shutt mini-tip straight forceps (2.75 mm diameter, Linvatec, Fl. USA) were used through the anteromedial portal to take a superficial mid-substance biopsy of the hamstring tendon graft bundle. Size of the biopsies was 2-3 mm.

In order to create a timeline of ACL autograft remodelling belonging to different individuals, samples were allocated to one of the following groups depending on the time point of their retrieval after ACL reconstruction: group 1 = 6-12 months, group 2 = 13-24 months, group 3 = greater than 24 months. Two control groups were made: native hamstring tendon (HT) and native ACL. The HT control group biopsies were taken in patients (nonrelated to groups 1-3) at the end of ACL reconstructive surgery. A biopsy was taken from the excess of the hamstring autograft exiting the tibia tunnel after tensioning and fixation of the graft. This excess tendon was normally discarded. The ACL control biopsies were taken from patients (nonrelated to groups 1-3) who underwent ACL reconstruction after an acute femoral ACL tear (not later than 8 weeks after injury). Therefore, it was possible to obtain tissue samples from noninjured mid-substance areas. All patients gave written consent that tissue samples were allowed to be obtained and to be processed histologically. After the biopsies were taken, the remaining tissue was removed to continue with the ACL reconstruction procedure.

Directly after retrieval, samples were fixed in formalin for 2 to 3 days, automatically dehydrated for 3 days and embedded in paraffin. Serial cuts (4 µm) were prepared and mounted on slides with 3% silane (Sigma Chemical, St. Louis, MO, USA).
For descriptive and quantitative cell analysis, haematoxylin-eosin (HE) and Masson-Goldner-Trichrom (MG) staining were used following standard histological protocols.

Vascular density was evaluated by immunostaining sections with a polyclonal rabbit antihuman von Willebrandt Factor (Factor VIII) antibody (cat.-no. M0851, Dako, Glostrup, Denmark). This antibody binds on the endothelial surface of blood vessels.
For the detection of myofibroblasts, tissue sections were immunostained with a mouse anti-human ASMA monoclonal antibody (cat. no. M0851, Dako, Glostrup, Denmark), which binds on α-smooth muscle actin (ά –sma) especially present in myofibroblasts.

All tissue samples were hydrated and pretreated with 0,1% pronase for 10 min at 37 °C for factor-VIII analysis. Myofibroblast detection did not require pretreatment. For both analyses, 10% normal horse serum (Vector Laboratories Inc., Burlington, CA, USA) was used for 20 min at room temperature to block nonspecific binding sites. The antibody was diluted 1:200 for factor-VIII and 1:100 for ά-sma and added to the tissue samples overnight in a humidity chamber at 4°C. After rinsing the samples with tris-buffered saline, they were incubated with the biotinylated horse anti-mouse immunoglobulin G secondary antibody for 30 min. This was followed by incubation with an avidin-biotin complex (ABC Kit, Vectors Laboratories Inc., Burlington, CA, USA) linked with alkaline phosphatase as a reporter enzyme for 50 min. Staining was achieved with Neurofuchsin as a chromogen. Tissues where counterstained with Mayers Haematoxylin, dehydrated, and mounted in a xylol-soluble mount (Vitroclud, R Langenbrinck, Emme Both Endingen, Germany).

For all assessments (cellularity density, vessel density and myofibroblast density), sections were automatically digitized and saved using a digital video analysis system (KS 400 3.0, Carl Zeiss AG, Göttingen, Germany). Ten regions of interest (ROI) of different sizes, depending on the sample size, were placed on the sample at random. Cells, vessels and myofibroblasts were counted per mm² at x100 power. Values are reported with 1 decimal. Myofibroblast were morphologically differentiated from perizytes. These cells vary by their cell shape, the proximity to vessels and show a different distribution between matrix fibres.

For descriptive analysis, cell distribution pattern (uniform/ not uniform), morphology (oblong/ spindled/rounded, ovoid) and the evidence of inflammatory reactions were analysed at x50, x100, x200 and x400 power. Collagen fibril alignment was also assessed.

Statistical analysis
A Shapiro–Wilks test was used to evaluate the normal distribution of all parameters of interest. Because of nonparametric distribution, the Kruskal Wallis test was performed for group comparison. The Pearsons' chi-square test was used for comparison of gender. Finally the Mann–Whitney U test was used to compare cellular density, vascular density and myofibroblast density pairwise between the three groups, native HT and native ACL. Results were corrected with Bonferroni–Holm correction. Level of significance was set at $P \leq 0.05$.

Results

Total number of biopsies (one per patient) was 67: 15 biopsies in group 1 (6–12 months after ACL reconstruction), 16 in group 2 (13–24 months), 11 in group 3 (> 24 months), 17 HT controls and 8 ACL controls. Group 1–3 were statistically comparable for age, gender, activity level and results of the KT-1000 measurements (Table 1).

Table 2 shows the detailed results for cell-, vessel- and myofibroblast density for all biopsy groups. Compared to native HT, total cell number was significantly increased in groups 1–3 (group 1: $P = 0.036$; group 2: $P = 0.005$ and group 3: $P = 0.043$). The highest value was found at 13–24 months (Fig. 1). Total cell number decreased from group 2 to 3 without reaching the cell density level of the native ACL (non-significant n.s.).

Fig. 2 illustrates the results for vessel density. Vessel density showed the lowest value in group 1. Consecutively, vessel density increased up to the level of native HT in group 2 and higher values in group 3, without reaching the vessel density of the native ACL at any time point (n.s.). Comparing the controls, HT had a lower vessel density than ACL (n.s.).

The results for myofibroblast density are illustrated in Fig. 3. Myofibroblast density was significantly higher in group 2 compared with native HT ($P = 0.014$). Myofibroblast density increased from group 1 to group 2 (n.s.). From group 2 to 3, myofibroblast density decreased but was still increased compared to both controls (n.s.).

Fig. 4 demonstrates myofibroblast histology in the 3 study groups. Necrosis was absent in the biopsies. Collagen orientation was irregular up to 12 months. Thereafter, collagen orientation became more regular, adapting to, but not fully restoring the appearance of the intact ACL. For the first 12 months, cells were predominantly ovoid. Ensuing cell morphology changed to spindle-shaped in group 2 and predominantly narrow long cells over 24 months (Fig. 5). Collagen orientation did not return to normal in the study period.

Discussion

The most important finding of the present study was that human hamstring autografts showed typical stages of graft remodelling, which was not complete up to 2 years after ACL reconstruction.

Animal studies have analysed tendon remodelling in bone tunnels in relation to the type of fixation after ACL reconstruction.[7, 16, 24, 29, 30]
Weiler et al. found that biodegradable interference screw fixation of a soft tissue graft may alter the mechanical properties in the early remodelling stage because of tissue compromise at the screw insertion site.[30]

Singhatat et al.[24] examined early strength and stiffness of soft tissue fixation comparing biodegradable interference screw versus WasherLoc (Arthrotec, Warsaw, IN, USA) fixation at 4 weeks. The strength and stiffness of the complex deteriorated after 4 weeks of implantation with the interference screw, but was either maintained or improved with use of the WasherLoc device. They postulated that aggressive rehabilitation after ACL reconstruction should only be allowed after ACL reconstruction with a fixation device that maintains strength and stiffness in the first few weeks of implantation.[24] In the present study, the WasherLoc device was used as tibial fixation of the hamstring tendon autograft. All patients followed a standardized accelerated rehabilitation protocol.

Other animal studies have analysed the intra-articular remodelling process of different graft types after ACL replacement. The autograft underwent necrosis, revascularization, and remodelling over time. Return of overall graft integrity and histological appearance was completed 6–12 months after reconstruction without full restoration of the mechanical strength of the intact ACL.[4, 8, 25, 26, 31] Grafts approached only 50–60% of the intact ACL failure strength.[1, 13, 21, 31]

Human biopsy studies have been performed with various techniques, to analyse remodelling of autografts after ACL reconstruction.[6, 11, 18, 19, 35]
Marumo et al.[11] performed a biochemical study to analyse remodelling of 30 patellar tendon and 20 hamstring autografts after ACL reconstruction. They analysed collagen content and the amount of reducible and non-reducible crosslinks. Hamstring autograft biopsies were taken at 4- to 6-month and 11- to 13-month intervals. Native ACL, patellar tendon, gracilis and semitendinosus biopsies served as controls (fresh cadavers). They concluded that, based on amount of collagen crosslinks and their architecture, remodelling occurs within one year after ACL reconstruction. The graft did not gain sufficient mechanical functionality. They hypothesized that a low-aggressive rehabilitation programme might seem more desirable although this was not specifically examined in their study.[11] Their method of tissue biopsy was comparable with the technique of the present study. Both studies examined mid-substance biopsies for analysis of remodelling of hamstring autografts in clinically successful ACL reconstructions.
In contrast to the study of Marumo et al.[11], the present study used a standardized surgical technique with autograft hamstring tendons and a standardized accelerated rehabilitation protocol. Analysis of cellular density, vascular density and myofibroblast density indicated a prolonged remodelling process compared to their study.

Zaffagnini et al.[35] took 10 mid-substance biopsies of patellar tendon autografts from 6 months to 10 years after ACL reconstruction. Two patellar tendons and two ACL's served as controls (fresh cadavers). They performed a qualitative and quantitative histological evaluation of collagen fibrils by means of transmission electron microscopy. The patellar tendon autograft underwent a transformation period up to 2 years without reaching the mean diameter and bimodality of a native ACL.[35] In the present study, hamstring tendon autograft biopsies were examined by immunohistochemical evaluation of cellular density, vascular density and myofibroblast density. Despite the differences in methodology, we agree with their findings that human remodelling was prolonged compared to animal studies.

Rougraff et al.[18] took 23 biopsies, 0.75–78 months after patellar tendon autograft ACL reconstruction. They found four stages of ligamentization, but duration and evolution of ligamentization was different from animal studies. In the first phase (1–2 months), there was a moderate increase in fibroblasts and start of vascular ingrowth. The excessive graft necrosis observed in animal studies could not be confirmed in humans, where necrosis never involved more than 30% of the graft's biopsies. During the second phase (2–10 months), increase of metabolic active fibroblasts, vessels and irregular collagen fibres occurred. From 1–3 years, fibroblast and vessel density decreased. Grafts showed histology similar to a ligament without reaching normal ligament cell or vessel density levels. At 3 years, these levels were achieved.[18] In the present study, the earliest biopsy was taken 6 months after ACL reconstruction. This might explain the absence of necrosis since it would be expected in an earlier stage of remodelling.[20]

Falconiero et al.[6] analysed 48 biopsies from human patella and hamstring tendons, 3–120 months after ACL replacement. They concluded that remodelling was completed 12 months after ACL reconstruction because no significant differences for vascularity and fibre pattern were evident. They postulated that their results may support early postoperative return to full activity and an accelerated rehabilitation programme.[6]

Contrary to the results of Rougraff et al.[18] and Falconiero et al.[6], the present study found an increasing cell and vessel density up to 24 months. Especially the strong increase in myofibroblast density, from 13 up to 24 months, indicated an active remodelling process from 1 to 2 years. Furthermore, vessel density increased over 24 months whereas cell and myofibroblast density decreased but stayed higher compared with native controls.

Recent work by Sánchez et al.[19] focused on ligamentization of hamstring autografts treated with platelet-rich plasma preparation rich in growth factors (PRGF) after ACL reconstruction. Thirty-seven biopsies were taken 6-24 months after ACL reconstruction. The PRGF-treated grafts showed more remodelling compared with untreated grafts. At 14-18 months, the uniform linear collagen orientation and the spindle-shaped morphology of the native hamstring tendon differed from the remodelled collagen and the ovoid cells present after ligamentization. Specific information on the duration of the ligamentization process was not described.[19]

In the present study, a remodelling process was also evident. In contrast to the aforementioned human biopsy studies, special immunohistochemical staining techniques were performed to detect vessel- and myofibroblast density. Unterhauser et al. showed that the factor-VIII staining can improve vessel detection possibility.[26] Myofibroblasts are known to be important cells during the remodelling process of ACL grafts. Their appearance is described as typical for this process.[5, 26] The increasing myofibroblast density between 13 and 24 months in the present study indicated that the remodelling process in humans was prolonged compared with the results obtained in several animal studies.

In light of the current insights into ACL surgery, the transtibial technique in the present study was a nonanatomic ACL reconstruction. As a result, knee joint motion will not provide the same mechanical stimulus to the healing ACL graft as to the intact ACL.[3, 10, 28, 32-34] Scheffler et al. presented the importance of restoring knee joint mechanics for graft remodelling after ACL reconstruction in order to replicate the loading conditions of the intact ACL.[20] This might explain the prolonged remodelling process in the present study.

There are some limitations to the study.
There were no biopsies earlier than 6 months after ACL reconstruction. Therefore, analysis of the early stage of remodelling could not be performed. It was not possible to study ACL remodelling by subsequent hamstring autograft biopsies in the same individuals. Therefore, it was not possible to verify whether changes occurring in grafts from one time point to another, may partially be attributed to amongst-subject variation. The present study was limited to small biopsies of the periphery of the ACL graft. It did not provide information on the remodelling process in the graft centre. Finally, the crimp pattern could not be assessed due to the small biopsies compared to animal study models.

Knowledge about the duration of remodelling process of ACL grafts may influence and improve outcome as well as rehabilitation protocols.[11, 20] This is the first study to document remodelling of human hamstring autografts in relation to a standardized surgical technique and standardized accelerated rehabilitation. The clinical relevance of the study is that, based on the prolonged remodelling of human hamstring grafts, it may be questionable whether accelerated rehabilitation after nonanatomic ACL reconstruction is to be recommended. Future research should focus on the remodelling process of hamstring grafts in an anatomic ACL reconstruction.

Conclusion

Human hamstring grafts showed typical stages of graft remodelling which was not complete up to 2 years after ACL reconstruction. The remodelling process in humans was prolonged compared with the results obtained in several animal studies.

Acknowledgement
The authors would like to thank Ineke van Lijnschoten MD, PhD, pathologist for all her efforts in the early analysis and histological preparation of the biopsies.

Table 1

Demographics (age, gender) of all study groups and KT-1000 results (133 N difference between injured and non-injured leg)

	Age Median Mean	(range) (SD)		Gender (m/f)		KT 1000 133 N Inj. - Non-inj. Mean (SD)	
Group 1	28.0	(19–54)	*P* = 0.461	9/6	*P* = 0.932	0.8	(0.8)
<12 months (*n* = 15)	31.1	(11.8)					
Group 2	25.5	(17–46)		10/6		0.6	(0.7)
13–24 months (*n* = 16)	27.7	(8.7)					
Group 3	29.0	(21–37)		7/10		1.0	(0.8)
>24 months (*n* = 11)	29.0	(6.3)					

Table 2

Results of all biopsy groups for cellular density, vessel density and myofibroblast density

	Group 1	Group 2	Group 3	HT control	ACL control
Cells/mm²					
Mean	736.3	789.5	718.2	327.6	535.8
Range	1550.7	1243.5	1173.2	663.3	1545.9
Median	482.0	850.9	595.6	330.4	371.9
SD	454.1	371.1	386.9	201.6	489.4
Vessels/mm²					
Mean	17.9	6.1	8.2	7.4	11.9
Range	181.8	41.9	22.6	67.7	31.5
Median	0.0	3.4	3.6	3.1	10.1
SD	47.3	10.3	8.5	15.9	9.3
Myofibroblast/mm²					
Mean	35.6	224.1	207.9	3.4	5.7
Range	144.7	820.6	815.0	14.6	25.7
Median	11.5	199.6	97.7	1.9	1.4
SD	47.3	234.4	275.3	4.4	8.9

Fig. 1 Results of the median cellular density for all biopsy groups.

Significant differences between groups 1–3 and native hamstring tendon are illustrated with *

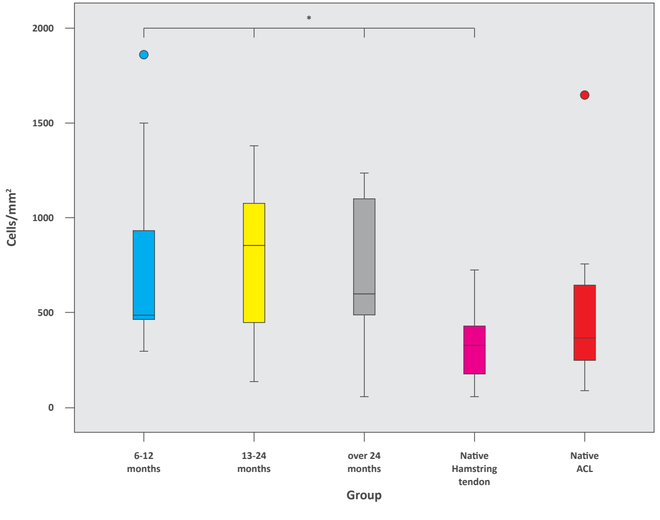


Fig. 2 Results of median vessel density for all biopsy groups

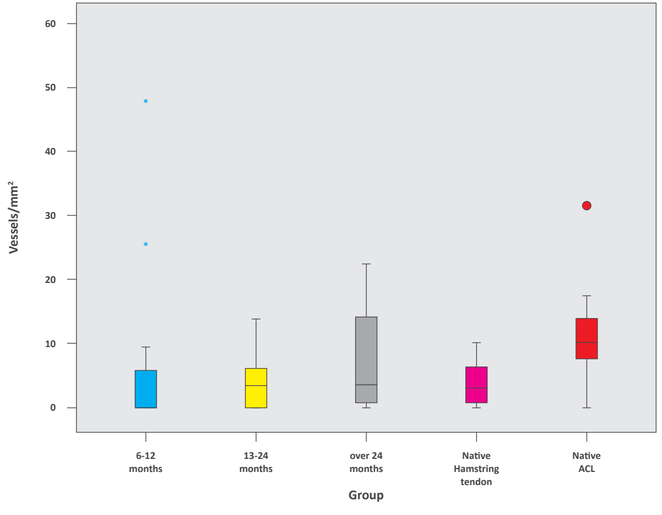


Fig. 3 Results for median myofibroblast density for all biopsy groups.

Myofibroblast density was significantly higher in group 2 (13–24 months) compared with native HT control (marked with *)

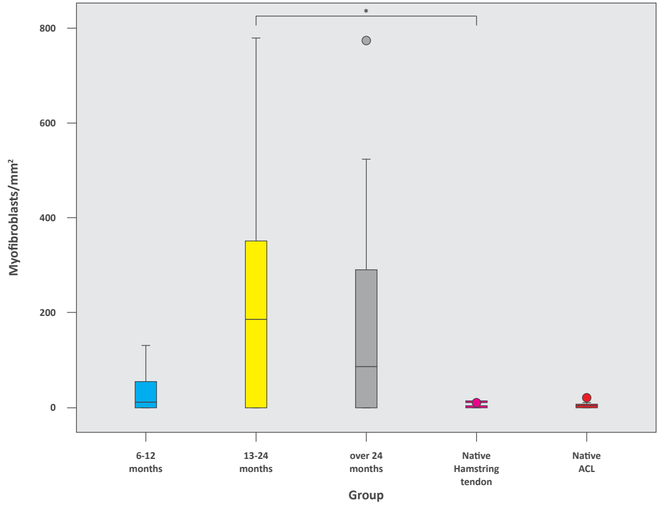


Fig. 4

Alpha-smooth staining: Group 1 (top left) showed a moderate number of myofibroblasts compared with groups 2 and 3 (right and down). Note an increased number of myofibroblast and vessels in groups 2 and 3

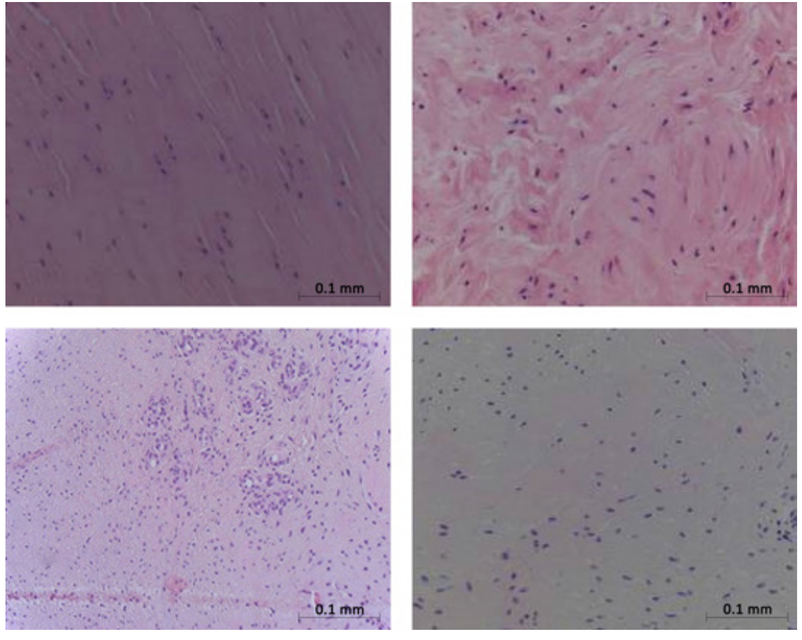
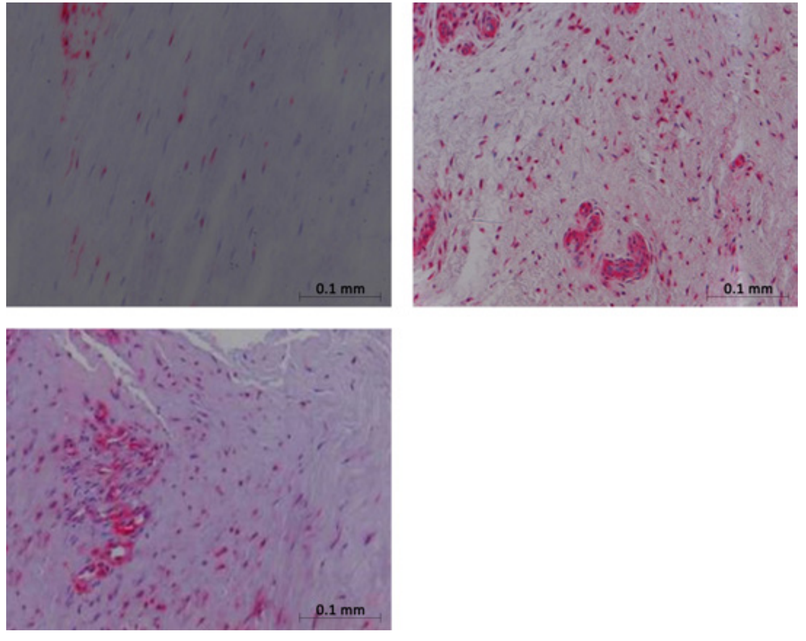


Fig. 5

HE staining: hamstring tendon (top left) with regular collagen orientation, moderate cellular density and little fibroblast activity. Group 1 (top right): irregular collagen alignment, increased cellular density, ovoid cell morphology. Group 2 (below left): further increased cellular and vessel density with an irregular collagen orientation. Group 3 (below right): improved regular collagen arrangement



References

1. Amiel D, Kleiner JB, Roux RD, Harwood FL, Akeson WH (1986) The phenomenon of "ligamentization": anterior cruciate ligament reconstruction with autogenous patellar tendon. J Orthop Res 4(2):162–172

2. Andersson C, Odensten M, Gillquist J (1991) Knee function after surgical or nonsurgical treatment of acute rupture of the anterior cruciate ligament: a randomized study with a long-term follow-up period. Clin Orthop Relat Res (264):255–263

3. Arnold MP, Kooloos J, van Kampen A (2001) Single-incision technique misses the anatomical femoral anterior cruciate ligament insertion: a cadaver study. Knee Surg Sports Traumatol Arthrosc 9(4):194–199

4. Clancy WG, Jr., Narechania RG, Rosenberg TD, Gmeiner JG, Wisnefske DD, Lange TA (1981) Anterior and posterior cruciate ligament reconstruction in rhesus monkeys. J Bone Joint Surg Am 63(8):1270–1284

5. Dustmann M, Schmidt T, Gangey I, Unterhauser FN, Weiler A, Scheffler SU (2008) 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 Surg Sports Traumatol Arthrosc 16(4):360–369

6. Falconiero RP, DiStefano VJ, Cook TM (1998) Revascularization and ligamentization of autogenous anterior cruciate ligament grafts in humans. Arthroscopy 14(2):197–205

7. Goradia VK, Rochat MC, Kida M, Grana WA (2000) Natural history of a hamstring tendon autograft used for anterior cruciate ligament reconstruction in a sheep model. Am J Sports Med 28(1):40–46

8. Goradia VK, Rochat MC, Grana WA, Rohrer MD, Prasad HS (2000) Tendon-to-bone healing of a semitendinosus tendon autograft used for ACL reconstruction in a sheep model. Am J Knee Surg 13(3):143–151

9. Gulotta LV, Rodeo SA (2007) Biology of autograft and allograft healing in anterior cruciate ligament reconstruction. Clin Sports Med 26(4):509–524

10. Kopf S, Forsythe B, Wong AK, Tashman S, Anderst W, Irrgang JJ, Fu FH (2010) Nonanatomic tunnel position in traditional transtibial single-bundle anterior cruciate ligament reconstruction evaluated by three-dimensional computed tomography. J Bone Joint Surg Am 92(6):1427–1431

11. Marumo K, Saito M, Yamagishi T, Fujii K (2005) The "ligamentization" process in human anterior cruciate ligament reconstruction with autogenous patellar and hamstring tendons: a biochemical study. Am J Sports Med 33(8):1166–1173

12. Menetrey J, Duthon VB, Laumonier T, Fritschy D (2008) "Biological failure" of the anterior cruciate ligament graft. Knee Surg Sports Traumatol Arthrosc 16(3):224–231

13. Ng GY, Oakes BW, Deacon OW, McLean ID, Lampard D (1995) Biomechanics of patellar tendon autograft for reconstruction of the anterior cruciate ligament in the goat: three-year study. J Orthop Res 13(4):602–608

14. Panni AS, Milano G, Lucania L, Fabbriciani C (1997) Graft healing after anterior cruciate ligament reconstruction in rabbits. Clin Orthop Relat Res (343):203–212

15. Poolman RW, Abouali JA, Conter HJ, Bhandari M (2007) Overlapping systematic reviews of anterior cruciate ligament reconstruction comparing hamstring autograft with bone-patellar tendon-bone autograft: why are they different? J Bone Joint Surg Am 89A(7):1542–1552

16. Rodeo SA, Arnoczky SP, Torzilli PA, Hidaka C, Warren RF (1993) Tendon-healing in a bone tunnel. A biomechanical and histological study in the dog. J Bone Joint Surg Am 75(12):1795–1803

17. Roseti L, Buda R, Cavallo C, Desando G, Facchini A, Grigolo B (2008) Ligament repair: a molecular and immunohistological characterization. J Biomed Mater Res A 84(1): 117–127

18. Rougraff B, Shelbourne KD, Gerth PK, Warner J (1993) Arthroscopic and histologic analysis of human patellar tendon autografts used for anterior cruciate ligament reconstruction. Am J Sports Med 21(2):277–284

19. Sanchez M, Anitua E, Azofra J, Prado R, Muruzabal F, Andia I (2010) Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: gross morphology and histology. Arthroscopy 26(4):470–480

20. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16(9):834–842

21. Scheffler SU, Schmidt T, Gangey I, Dustmann M, Unterhauser F, Weiler A (2008) Fresh-frozen free-tendon allografts versus autografts in anterior cruciate ligament reconstruction: delayed remodeling and inferior mechanical function during long-term healing in sheep. Arthroscopy 24(4):448–458

22. Scranton PE, Jr., Lanzer WL, Ferguson MS, Kirkman TR, Pflaster DS (1998) Mechanisms of anterior cruciate ligament neovascularization and ligamentization. Arthroscopy 14(7):702–716

23. Seitz H, Menth-Chiari WA, Lang S, Nau T (2008) Histological evaluation of the healing potential of the anterior cruciate ligament by means of augmented and non-augmented repair: an in vivo animal study. Knee Surg Sports Traumatol Arthrosc 16(12):1087–1093

24. Singhatat W, Lawhorn KW, Howell SM, Hull ML (2002) How four weeks of implantation affect the strength and stiffness of a tendon graft in a bone tunnel: a study of two fixation devices in an extraarticular model in ovine. Am J Sports Med 30(4):506–513

25. Tohyama H, Yasuda K, Uchida H (2006) Is the increase in type III collagen of the patellar tendon graft after ligament reconstruction really caused by "ligamentization" of the graft? Knee Surg Sports Traumatol Arthrosc 14(12):1270–1277

26. Unterhauser FN, Bail HJ, Hoher J, Haas NP, Weiler A (2003) Endoligamentous revascularization of an anterior cruciate ligament graft. Clin Orthop Relat Res (414):276–288

27. Vairo GL, Myers JB, Sell TC, Fu FH, Harner CD, Lephart SM (2008) Neuromuscular and biomechanical landing performance subsequent to ipsilateral semitendinosus and gracilis autograft anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16(1):2–14

28. Voos JE, Musahl V, Maak TG, Wickiewicz TL, Pearle AD (2010) Comparison of tunnel positions in single-bundle anterior cruciate ligament reconstructions using computer navigation. Knee Surg Sports Traumatol Arthrosc 18(9):1282–1289

29. Weiler A, Hoffmann RF, Bail HJ, Rehm O, Sudkamp NP (2002) Tendon healing in a bone tunnel. Part II: Histologic analysis after biodegradable interference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. Arthroscopy 18(2):124–135

30. Weiler A, Peine R, Pashmineh-Azar A, Abel C, Sudkamp NP, Hoffmann RF (2002) Tendon healing in a bone tunnel. Part I: Biomechanical results after biodegradable interference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. Arthroscopy 18(2):113–123

31. Xu Y, Ao YF (2009) Histological and biomechanical studies of inter-strand healing in four-strand autograft anterior cruciate ligament reconstruction in a rabbit model. Knee Surg Sports Traumatol Arthrosc 17(7):770–777

32. Yagi M, Wong EK, Kanamori A, Debski RE, Fu FH, Woo SL (2002) Biomechanical analysis of an anatomic anterior cruciate ligament reconstruction. Am J Sports Med 30(5):660–666

33. Yamamoto Y, Hsu WH, Woo SL, Van Scyoc AH, Takakura Y, Debski RE (2004) Knee stability and graft function after anterior cruciate ligament reconstruction: a comparison of a lateral and an anatomical femoral tunnel placement. Am J Sports Med 32(8):1825–1832

34. Yoon KH, Bae DK, Cho SM, Park SY, Lee JH (2009) Standard anterior cruciate ligament reconstruction versus isolated single-bundle augmentation with hamstring autograft. Arthroscopy 25(11):1265–1274

35. Zaffagnini S, De Pasquale V, Marchesini Reggiani L, Russo A, Agati P, Bacchelli B, Marcacci M (2007) Neoligamentization process of BTPB used for ACL graft: histological evaluation from 6 months to 10 years. Knee 14(2):87–93

INTRA-ARTICULAR REMODELLING OF HAMSTRING TENDON GRAFTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Rob P.A. Janssen and Sven U. Scheffler

Knee Surgery, Sports Traumatology, Arthroscopy 2014;22:2102–2108

6

Abstract

Purpose
A summary is provided on the existing knowledge about the specific healing phases of the intra-articular hamstring tendon graft used for ACL reconstruction. Differences between human and animal in vivo studies are explained and implications for the postoperative time period are laid out.

Methods
A systematic review of the existing literature was performed on the topic of tendon remodelling of hamstring grafts in ACL reconstruction using Medline database. Publications between 1982 and 2012 were included. Special focus was directed on in vivo human and animal studies analysing intra-articular free tendon graft remodelling.

Results
Animal and human in vitro and vivo research have demonstrated three characteristic stages of graft healing after ACL reconstruction: an early graft healing phase with central graft necrosis and hypocellularity and no detectable revascularization of the graft tissue, followed by a phase of proliferation, the time of most intensive remodelling and revascularization and finally, a ligamentization phase with characteristic restructuring of the graft towards the properties of the intact ACL. However, a full restoration of either the biological or biomechanical properties of the intact ACL is not achieved.

Conclusion
Significant knowledge on human cruciate ligament remodelling has been added in the understanding of the processes during the course of graft healing. Most importantly, the remodelling process in humans is prolonged compared to animal studies. While today´s rehabilitation protocols are often extrapolated from findings of animal in vivo healing studies, current findings of human in vivo healing studies might require new postoperative regimens following hamstring ACL reconstruction.

Keywords
Graft remodelling · ACL · Hamstring tendon · Accelerated rehabilitation · Ligamentization

Level of evidence III

Introduction

Anterior cruciate ligament (ACL) reconstruction techniques have been improved over the last 10 years, but graft failure is not uncommon: 0.7–10%.[24, 35]

Successful ACL reconstruction requires understanding of several factors: anatomical graft placement, mechanical properties of the selected graft tissue, mechanical behaviour and fixation strength of fixation materials as well as the biological processes that occur during graft remodelling, maturation and incorporation. They influence directly the mechanical properties of the knee joint after ACL reconstruction and, therefore, determine the rehabilitation and time course until normal function of the knee joint can be expected.[10, 12, 24, 32–34, 41, 45, 57]
Even though substantial research efforts have been published on various aspects of ACL reconstruction, there is limited knowledge on the biology of the human ACL graft.[10, 12, 13, 15, 19, 24, 30, 32, 44–46, 48, 57, 58, 63, 65, 66]

Graft healing after ACL reconstruction occurs at two different sites: intra-tunnel graft incorporation[59, 61] and intra-articular graft remodelling, often referred to as "ligamentization".[4, 10, 24, 30, 32, 33, 44, 45, 53] This article presents the current knowledge on intra-articular remodelling of ACL grafts with special focus on human hamstring autografts.

Phases of remodelling

Animal and human in vitro and vivo research have demonstrated three characteristic stages of graft healing after ACL reconstruction: an early graft healing phase with central graft necrosis and hypocellularity and no detectable revascularization of the graft tissue, followed by a phase of proliferation, the time of most intensive remodelling and revascularization and finally, a ligamentization phase with characteristic restructuring of the graft towards the properties of the intact ACL.[2–4, 24, 28, 32, 36, 43, 65, 66] However, a full restoration of either the biological or mechanical properties of the intact ACL is not achieved.[2, 4, 45]

Early graft healing phase
This phase is defined as the period from the time of ACL reconstruction until the fourth postoperative week.

It is marked by increasing necrosis, mainly in the centre of the graft and hypocellularity.[2, 4, 27, 45, 51] An influx of host cells can be seen into the graft's periphery between the first and second week.[27, 28] The source of these cells is thought to be the synovial fluid, cells from the stump of the native ACL or bone marrow elements originating from drilling the tunnels. Preservation of the ACL stump and Hoffa fat pad may be beneficial for graft healing in this phase.[5, 15, 41]

At the same time, no graft revascularization can be observed.[5, 28, 50, 64] Even though beginning disintegration of collagen fibrils and their orientation can be observed as early as 3 weeks after reconstruction[16], the graft's overall collagen structure and crimp pattern are maintained.[2, 4] This explains the slow decrease in the mechanical properties of the graft in this early healing phase.[40, 45, 50]
During this early healing phase, between 2 and 4 weeks, the lack of sufficient biological graft incorporation is the weak site of the reconstruction with consistent failure by graft pullout[16, 17, 40, 62], therefore requiring and relying on appropriate mechanical graft fixation. A shift towards the intra-articular graft region becoming the weak link is noted during the proliferation healing phase when the maximum remodelling activity seems to interfere with the mechanical strength of the healing graft.[16, 40, 58]

Proliferation phase of graft healing
The proliferation phase is defined as the period between 4–12 weeks after ACL reconstruction.
This phase is characterized by maximum cellular activity and changes of the extracellular matrix, which are paralleled by the lowest mechanical properties of the reconstructed ACL graft. Graft necrosis leads to a release of growth factors, which stimulate cell migration and proliferation as well as extracellular matrix synthesis and revascularization.[22, 26, 29, 51, 64]

An increased number of specific fibroblasts, so-called myofibroblasts appear. They are responsible for the restoration of the in situ tension that is required for the later ligamentization phase.[36, 45, 55, 60] At the end of the proliferation phase, cell density is still increased, but recedes towards the intact ACL's cellularity.[6, 21, 24, 45, 51, 56, 62]

Revascularization of the graft starts from the fourth postoperative week[5, 45, 56, 58] progressing from the periphery of the graft to the entire graft diameter at 12 weeks.[42, 56]

Animal studies have shown that the mechanical properties of the graft are at its weakest at 6–8 weeks. Three factors contribute to the decline in the graft's mechanical properties: (a) increased revascularization and extracellular infiltration, (b) loss of regular collagen orientation and crimp pattern and (c) decrease in collagen fibril density, followed by increased collagen synthesis with a shift from large-diameter collagen fibrils to small-diameter fibrils.[6, 9, 16, 20, 21, 28, 45, 51, 52, 54, 58, 61, 62] Furthermore, increased collagen III synthesis (with lower mechanical strength than type I collagen) may further explain why a full restoration of the mechanical strength of the intact ACL has not been observed in any in vivo model even after 2 years of healing.[34, 42, 45, 52]

The reduced mechanical properties of healing grafts in animal models seem to contradict the successful clinical outcomes after ACL reconstruction with immediate aggressive rehabilitation in humans. Significant differences were found in biopsy studies between the remodelling activity of human ACL grafts during the first 3 months and the healing graft in animal models. The complete loss and replacement of all intrinsic graft has not been observed in human biopsy studies.[25, 43] The excessive graft necrosis in animals, could not be confirmed in humans, where necrosis or degeneration never involved more than 30% of the graft's biopsies.[25, 35, 43]
Neovascularization was not as excessive in humans.[25] Large areas of human healing graft stay unchanged displaying tendinous structure with normal collagen alignment and crimp pattern.[25] Loss of collagen organization was only detected in areas of neovascularization in human biopsies, which corresponds to the findings in animal studies.[24, 45]
However, human biopsy studies confirm the remodelling cascade of (limited) graft necrosis, recellularization, revascularization and changes in collagen crimp and composition during the early healing and proliferation phases, suggesting that also the human ACL graft might have its lowest mechanical strength around 6–8 weeks postoperatively.[43, 65] Loading of the graft must be high enough to stimulate graft cells to produce cellular and extracellular components for preservation of graft stability, but without compromising graft integrity, which might result into an early stretch-out of the ACL reconstruction.[45]

Ligamentization phase of graft healing
The ligamentization phase involves the continuous remodelling of the healing graft towards the morphology and mechanical strength of the intact ACL from 12 weeks onwards. A clear endpoint is not known for certain changes still occur even years after reconstruction.

In animal models, cellularity slowly returns to values of the intact ACL between 3–6 months postoperatively.[42, 45, 56, 58] Vascularity throughout the graft decreases and returns to values of the intact ACL between 6 and 12 months, when vessels become evenly distributed throughout the entire graft.[5, 45, 56, 58] Collagen fibres regain their organization, which microscopically resembles the appearance of the intact ACL around 6 and 12 months after reconstruction.[45, 60] However, the initial loss in collagen crimp and strict parallel alignment of the proliferation phase is only partially restored.[45, 60] The heterogenous composition of collagen fibres of varying diameter of the intact ACL is never restored.[1, 21, 31, 62]

It has been shown that the mechanical properties of the ACL reconstructed knee joint improve substantially during the phase of ligamentization and reach their maximum properties at around 1 year. However not a single animal study has demonstrated that the structural properties (e.g. failure load, stiffness) of the healing graft could surpass 50–60% of the intact ACL.[6, 9, 16, 21, 37, 38, 40, 45, 58, 61]

While human biopsy studies showed substantial differences from animal models during the proliferation phase, the ligamentization phase is rather similar in both models in terms of biological progression.
However, the timeline of these biological changes is different: studies in humans have shown a prolonged remodelling process compared to animal models.[10, 12, 24, 30, 32, 43–45, 53, 65, 66]

Remodelling of human hamstring autografts after ACL reconstruction

When interpreting animal data with regard to changes occurring in human autografts, important clinical factors such as graft isometricity, anatomical positioning, patient compliance, healing response, vascularity, biomechanical strength and postoperative rehabilitation must be considered. These factors are difficult to control in animal models. Nevertheless, the results of animal studies are important, because human research has been limited to post-mortem and second-look arthroscopic evaluation.[32] Research on remodelling of human hamstring autografts after ACL reconstruction can be divided into MRI studies and biopsy studies.[10, 12, 13, 15, 24, 30, 32, 44, 47, 57, 66] The current knowledge on remodelling of human hamstring ACL grafts and rehabilitation will be presented in the next sections.

MRI studies of human hamstring ACL grafts

MRI studies have examined the revascularization of human hamstring autografts after ACL reconstruction.[13, 15, 19, 57] In a gadolinium-enhanced MRI study, Howell et al.[19] did not demonstrate any discernible blood supply in an unimpinged 4-strand hamstring ACL graft during the 2 years of implantation. The graft retained the same hypovascular appearance as the normal posterior cruciate ligament. In contrast, the periligamentous soft tissues were richly vascularized and covered the graft by 1 month. They postulated that the viability of an unimpinged, human hamstring ACL graft may depend more on synovial diffusion than on revascularization.[19] This is in contrast to findings in animal studies, where gadolinium-enhanced MRI showed significant upregulated neovascularization during the first 3 postoperative months.[58] This underlines the differences in remodelling between humans and animal models.

Although human biopsy studies have shown that neovascularization of the hamstring graft occurs, the extent of vascularity in humans might be below the threshold detectable with gadolinium-enhanced MRI.[45] Gohil et al.[15] investigated the effect of minimal debridement of the stump of the ruptured ACL on revascularization of 4-strand human hamstring ACL autografts. They concluded that minimal debridement led to earlier revascularization within the midsubstance of the ACL graft at 2 months, but found no evidence that the minimal debridement accelerated the recovery of graft strength.[15]

Other authors examined the effect of autologous platelet concentrate on remodelling of 4-strand human hamstring ACL autografts with a standardized accelerated rehabilitation protocol. Vogrin et al. used contrast-enhanced MRI and found that revascularization of the graft only started at 4–6 weeks after ACL reconstruction.[57] Autologous platelet concentrate did not influence intra-articular remodelling of hamstring grafts.[13, 57] The revascularization of the human hamstring graft at 4–6 weeks correlates with the proliferation phase of graft healing.

Biopsy studies of human hamstring ACL grafts

Human biopsy studies have examined the remodelling process of the hamstring tendon autograft at various time intervals after clinically successful ACL reconstruction.[10, 12, 13, 24, 30, 32, 44, 47, 66] The human hamstring autograft remains viable after reconstruction and shows typical stages of remodelling: early phase graft healing, a proliferation phase and a ligamentization phase.[10, 12, 24, 44] Graft integrity is much less compromised during the early healing and proliferation phase in human ACL grafts, which might allow for the assumption that the mechanical properties are also substantially higher than in animal models during the first 3 postoperative months.[10, 25, 45]

Focus of human hamstring biopsy studies has been the proliferation and ligamentization phases of graft healing, as most biopsies were taken at second-look arthroscopies from 4 months onwards after ACL reconstruction. Janssen et al.[24] examined 67 patients who underwent retrieval of mid-substance biopsies after clinically successful 4-strand hamstring autograft ACL reconstruction with a standardized accelerated rehabilitation programme. Cellular density and vascular density were increased up to 24 months after ACL reconstruction. Especially the strong increase in myofibroblast density, from 13 up to 24 months, indicated an active remodelling process from 1 to 2 years (Fig. 1). Furthermore, vessel density increased over 24 months, whereas cell and myofibroblast density decreased but stayed higher than native hamstring and ACL controls. Collagen orientation did not return to normal in the study period (up to 117 months after ACL reconstruction).[24]

Human biopsy studies that analysed changes of the extracellular matrix observed changes that are in line with the findings of animal models. Marumo et al.[32] found that the collagen crosslinks of hamstring tendon autografts had changed from time zero, when they were significantly different from the intact ACL, to 1 year postoperatively, when both grafts had acquired crosslink ratios that were identical to the intact ACL, confirming the ligamentization process found in animal models.

Interestingly, biopsy specimens taken at 6 months still showed significantly different crosslink ratios of the healing grafts compared to the intact ACL, which is different from the earlier crosslink restoration found in animal models.[30, 32, 45] This also confirms the different timeline of the remodelling of human ACL grafts.

Zaffagnini et al.[66] confirmed the observations in animal models[22, 31, 58] that human hamstring ACL grafts showed a replacement of large- by small-diameter fibrils, which did not change even after more than 2 years.[66]

Sanchez et al.[44] showed that use of platelet-rich plasma preparation rich in growth factors (PRGF) in hamstring ACL autografts resulted in temporal histological changes during the 6- to 24-month postoperative period in comparison with non-PRGF treated grafts. Biopsies were taken from the periphery of the hamstring autograft and the authors question whether these ACL substitutes entirely replicate the full mechanical properties of the intact ACL.[44] A better understanding of the graft biology in human ACL reconstruction will depend on the possibility to obtain core biopsy samples of the grafts.[10]

In summary, human hamstring ACL autografts undergo a process of adaptation rather than full restoration of the intact ACL´s biological properties, which takes at least 1 year after reconstruction.

Human hamstring remodelling and rehabilitation

Knowledge about the duration of the remodelling process of ACL grafts may influence and improve rehabilitation protocols.[24, 32, 45] Arthroscopic findings and clinical results after hamstring ACL reconstruction are found to be satisfactory with both accelerated and less aggressive rehabilitation protocols.[7, 8, 18, 23, 24, 32]

Advantages of accelerated rehabilitation after ACL reconstruction are earlier normal function of the knee[7, 18, 49] and have ability to return to even most strenuous activities after primary ACL reconstruction at 6 months.[45] However, some authors found that early return to vigorous physical activity may increase the risk of greater knee laxity after ACL reconstruction.[14, 35]

Biological findings have shown that human hamstring ACL graft remodelling takes at least 1 year after ACL reconstruction and is prolonged compared to animal models, on which current rehabilitation protocols are based after ACL reconstruction.[11, 12, 24, 30, 32, 44, 45, 47, 55, 56, 58–62, 66] Based on these findings in their biopsy study, Janssen et al.[24] question whether accelerated rehabilitation is to be recommended after 4-strand hamstring autograft ACL reconstruction.

It is agreed that ACL graft healing can only progress if mechanical loading occurs, however the most adequate magnitude at the varying phases of healing is still not clarified.[35, 39, 45, 54] It is crucial to understand what rehabilitation activities might lead to excessive ACL tensioning and therefore must be avoided during the first 3 postoperative months.

No final conclusions can be drawn on the mechanical strength of healing ACL grafts in humans with no available techniques for in vivo measurement of their mechanical properties. Even though it is not fully understood what the exact mechanisms are that guide the remodelling process, it seems to be important that physiological knee joint mechanics are restored to provide the same mechanical stimulus to the healing ACL graft as to the intact ACL. This guides adequate remodelling that will maintain initial graft integrity and (partial) cell viability, while initiating cellular and extracellular proliferation and differentiation to adapt the graft to its new biological and mechanical environment.

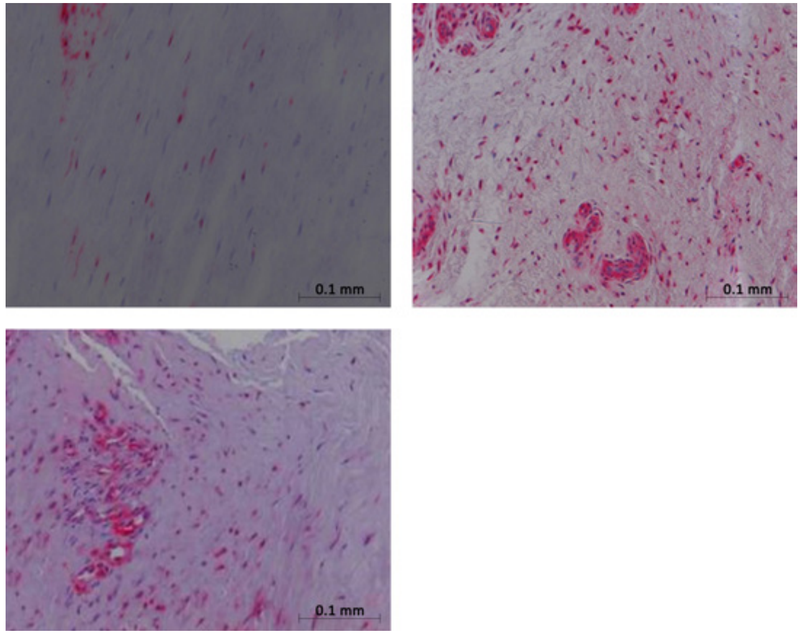
Conclusion

Hamstring tendon grafts remain viable after ACL reconstruction. The graft undergoes 3 characteristic stages of graft healing after ACL reconstruction: an early graft healing phase with limited graft necrosis and hypocellularity and no detectable revascularization of the graft tissue, followed by a phase of proliferation, the time of most intensive remodelling and revascularization and finally, a ligamentization phase with characteristic restructuring of the graft toward the properties of the intact ACL. An adaptation of the healing graft towards the intact ACL occurs without a full restoration of either the biological or mechanical properties of the intact ACL.

Future research will have to be directed to (a) optimizing cruciate ligament reconstructions to fully restore the anatomy and function while providing the mechanical strength of the intact cruciate ligaments, (b) developing biological treatment options that impact on graft healing especially during the early and proliferation phase to optimize extracellular matrix remodelling and avoid excessive remodelling activity that might impair mechanical integrity of the healing graft and (c) to better differentiate the 'good' from the 'bad' remodelling changes, so that the time to return to full activity without any restrictions can be reduced.

Fig. 1

Alpha-smooth staining biopsies of human hamstring ACL graft showing a moderate number of myofibroblasts 6–12 months (top left) compared to 13–24 months (top right) and over 24 months (bottom left) after ACL reconstruction. Note an increased number of myofibroblasts and vessels in biopsies at 13–24 months and over 24 months after ACL reconstruction (reproduced with permission from[24])



References

1. Abe S, Kurosaka M, Iguchi T, Yoshiya S, Hirohata K (1993) Light and electron microscopic study of remodeling and maturation process in autogenous graft for anterior cruciate ligament reconstruction. Arthroscopy 9(4):394–405

2. Amiel D, Kleiner JB, Akeson WH (1986) The natural history of the anterior cruciate ligament autograft of patellar tendon origin. Am J Sports Med 14(6):449–462

3. Amiel D, Frank C, Harwood F, Fronek J, Akeson W (1984) Tendons and ligaments: a morphological and biochemical comparison. J Orthop Res 1(3):257–265

4. Amiel D, Kleiner JB, Roux RD, Harwood FL, Akeson WH (1986) The phenomenon of "ligamentization": anterior cruciate ligament reconstruction with autogenous patellar tendon. J Orthop Res 4(2):162–172

5. Arnoczky SP, Tarvin GB, Marshall JL (1982) Anterior cruciate ligament replacement using patellar tendon. An evaluation of graft revascularization in the dog. J Bone Joint Surg Am 64(2):217–224

6. Ballock RT, Woo SL, Lyon RM, Hollis JM, Akeson WH (1989) Use of patellar tendon autograft for anterior cruciate ligament reconstruction in the rabbit: a long-term histologic and biomechanical study. J Orthop Res 7(4):474–485

7. Beynnon BD, Johnson RJ, Naud S, Fleming BC, Abate JA, Brattbakk B, Nichols CE (2011) Accelerated versus nonaccelerated rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind investigation evaluating knee joint laxity using roentgen stereophotogrammetric analysis. Am J Sports Med 39(12):2536–2548

8. Beynnon BD, Uh BS, Johnson RJ, Abate JA, Nichols CE, Fleming BC, Poole AR, Roos H (2005) Rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind comparison of programs administered over 2 different time intervals. Am J Sports Med 33(3):347–359

9. Blickenstaff KR, Grana WA, Egle D (1997) Analysis of a semitendinosus autograft in a rabbit model. Am J Sports Med 25(4):554–559

10. Claes S, Verdonk P, Forsyth R, Bellemans J (2011) The "ligamentization" process in anterior cruciate ligament reconstruction: what happens to the human graft? A systematic review of the literature. Am J Sports Med 39(11):2476–2483

11. Dustmann M, Schmidt T, Gangey I, Unterhauser FN, Weiler A, Scheffler SU (2008) 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 Surg Sports Traumatol Arthrosc 16(4):360–369

12. Falconiero RP, DiStefano VJ, Cook TM (1998) Revascularization and ligamentization of autogenous anterior cruciate ligament grafts in humans. Arthroscopy 14(2):197–205

13. Figueroa D, Melean P, Calvo R, Vaisman A, Zilleruelo N, Figueroa F, Villalon I (2010) Magnetic resonance imaging evaluation of the integration and maturation of semitendinosus-gracilis graft in anterior cruciate ligament reconstruction using autologous platelet concentrate. Arthroscopy 26(10):1318–1325

14. Fujimoto E, Sumen Y, Urabe Y, Deie M, Murakami Y, Adachi N, Ochi M (2004) An early return to vigorous activity may destabilize anterior cruciate ligaments reconstructed with hamstring grafts. Arch Phys Med Rehabil 85(2):298–302

15. Gohil S, Annear PO, Breidahl W (2007) Anterior cruciate ligament reconstruction using autologous double hamstrings: a comparison of standard versus minimal debridement techniques using MRI to assess revascularisation. A randomised prospective study with a one-year follow-up. J Bone Joint Surg Br 89(9):1165–1171

16. Goradia VK, Rochat MC, Grana WA, Rohrer MD, Prasad HS (2000) Tendon-to-bone healing of a semitendinosus tendon autograft used for ACL reconstruction in a sheep model. Am J Knee Surg 13(3):143–151

17. Grana WA, Egle DM, Mahnken R, Goodhart CW (1994) An analysis of autograft fixation after anterior cruciate ligament reconstruction in a rabbit model. Am J Sports Med 22(3):344–351

18. Howell SM, Taylor MA (1996) Brace-free rehabilitation, with early return to activity, for knees reconstructed with a double-looped semitendinosus and gracilis graft. J Bone Joint Surg Am 78(6):814–825

19. Howell SM, Knox KE, Farley TE, Taylor MA (1995) Revascularization of a human anterior cruciate ligament graft during the first two years of implantation. Am J Sports Med 23(1):42–49

20. Jackson DW, Grood ES, Cohn BT, Arnoczky SP, Simon TM, Cummings JF (1991) The effects of in situ freezing on the anterior cruciate ligament. An experimental study in goats. J Bone Joint Surg Am 73(2):201–213

21. Jackson DW, Grood ES, Goldstein JD, Rosen MA, Kurzweil PR, Cummings JF, Simon TM (1993) A comparison of patellar tendon autograft and allograft used for anterior cruciate ligament reconstruction in the goat model. Am J Sports Med 21(2):176–185

22. Jackson JR, Minton JA, Ho ML, Wei N, Winkler JD (1997) Expression of vascular endothelial growth factor in synovial fibroblasts is induced by hypoxia and interleukin 1beta. J Rheumatol 24(7):1253–1259

23. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM (2013) Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. Knee Surg Sports Traumatol Arthrosc 21(9):1977–1988

24. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299–1306

25. Johnson LL (1993) The outcome of a free autogenous semitendinosus tendon graft in human anterior cruciate reconstructive surgery: a histological study. Arthroscopy 9(2):131–142

26. Kawamura S, Ying L, Kim HJ, Dynybil C, Rodeo SA (2005) Macrophages accumulate in the early phase of tendon-bone healing. J Orthop Res 23(6):1425–1432

27. Kleiner JB, Amiel D, Roux RD, Akeson WH (1986) Origin of replacement cells for the anterior cruciate ligament autograft. J Orthop Res 4(4):466–474

28. Kleiner JB, Amiel D, Harwood FL, Akeson WH (1989) Early histologic, metabolic, and vascular assessment of anterior cruciate ligament autografts. J Orthop Res 7(2): 235–242

29. Kuroda R, Kurosaka M, Yoshiya S, Mizuno K (2000) Localization of growth factors in the reconstructed anterior cruciate ligament: immunohistological study in dogs. Knee Surg Sports Traumatol Arthrosc 8(2):120–126

30. Lane JG, McFadden P, Bowden K, Amiel D (1993) The ligamentization process: a 4 year case study following ACL reconstruction with a semitendinosis graft. Arthroscopy 9(2):149–153

31. Liu SH, Yang RS, al-Shaikh R, Lane JM (1995) Collagen in tendon, ligament, and bone healing. A current review. Clin Orthop Relat Res (318):265–278

32. Marumo K, Saito M, Yamagishi T, Fujii K (2005) The "ligamentization" process in human anterior cruciate ligament reconstruction with autogenous patellar and hamstring tendons: a biochemical study. Am J Sports Med 33(8):1166–1173

33. Mayr HO, Stoehr A, Dietrich M, von Eisenhart-Rothe R, Hube R, Senger S, Suedkamp NP, Bernstein A (2012) Graft-dependent differences in the ligamentization process of anterior cruciate ligament grafts in a sheep trial. Knee Surg Sports Traumatol Arthrosc 20(5):947–956

34. McFarland EG (1993) The biology of anterior cruciate ligament reconstructions. Orthopedics 16(4):403–410

35. Menetrey J, Duthon VB, Laumonier T, Fritschy D (2008) "Biological failure" of the anterior cruciate ligament graft. Knee Surg Sports Traumatol Arthrosc 16(3):224–231

36. Murray MM, Martin SD, Martin TL, Spector M (2000) Histological changes in the human anterior cruciate ligament after rupture. J Bone Joint Surg Am 82-A(10): 1387–1397

37. Ng GY, Oakes BW, Deacon OW, McLean ID, Lampard D (1995) Biomechanics of patellar tendon autograft for reconstruction of the anterior cruciate ligament in the goat: three-year study. J Orthop Res 13(4):602–608

38. Ng GY, Oakes BW, Deacon OW, McLean ID, Eyre DR (1996) Long-term study of the biochemistry and biomechanics of anterior cruciate ligament-patellar tendon autografts in goats. J Orthop Res 14(6):851–856

39. Ohno K, Yasuda K, Yamamoto N, Kaneda K, Hayashi K (1993) Effects of complete stress-shielding on the mechanical properties and histology of in situ frozen patellar tendon. J Orthop Res 11(4):592–602

40. Papageorgiou CD, Ma CB, Abramowitch SD, Clineff TD, Woo SL (2001) A multidisciplinary study of the healing of an intraarticular anterior cruciate ligament graft in a goat model. Am J Sports Med 29(5):620–626

41. Papalia R, Franceschi F, Vasta S, Di Martino A, Maffulli N, Denaro V (2012) Sparing the anterior cruciate ligament remnant: is it worth the hassle? Br Med Bull 104: 91–111

42. Petersen W, Unterhauser F, Pufe T, Zantop T, Sudkamp NP, Weiler A (2003) The angiogenic peptide vascular endothelial growth factor (VEGF) is expressed during the remodeling of free tendon grafts in sheep. Arch Orthop Trauma Surg 123(4):168–174

43. Rougraff BT, Shelbourne KD (1999) Early histologic appearance of human patellar tendon autografts used for anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 7(1):9–14

44. Sanchez M, Anitua E, Azofra J, Prado R, Muruzabal F, Andia I (2010) Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: gross morphology and histology. Arthroscopy 26(4):470–480

45. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16(9):834–842

46. Scheffler SU, Scherler J, Pruss A, von Versen R, Weiler A (2005) Biomechanical comparison of human bone-patellar tendon-bone grafts after sterilization with peracetic acid ethanol. Cell Tissue Bank 6(2):109–115

47. Scranton PE, Jr., Lanzer WL, Ferguson MS, Kirkman TR, Pflaster DS (1998) Mechanisms of anterior cruciate ligament neovascularization and ligamentization. Arthroscopy 14(7):702–716

48. Seitz H, Menth-Chiari WA, Lang S, Nau T (2008) Histological evaluation of the healing potential of the anterior cruciate ligament by means of augmented and non-augmented repair: an in vivo animal study. Knee Surg Sports Traumatol Arthrosc 16(12): 1087–1093

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

50. Shino K, Horibe S (1991) Experimental ligament reconstruction by allogeneic tendon graft in a canine model. Acta Orthop Belg 57 Suppl 2:44–53

51. Shino K, Kawasaki T, Hirose H, Gotoh I, Inoue M, Ono K (1984) Replacement of the anterior cruciate ligament by an allogeneic tendon graft. An experimental study in the dog. J Bone Joint Surg Br 66(5):672–681

52. Spindler KP, Andrish JT, Miller RR, Tsujimoto K, Diz DI (1996) Distribution of cellular repopulation and collagen synthesis in a canine anterior cruciate ligament autograft. J Orthop Res 14(3):384–389

53. Stener S, Ejerhed L, Movin T, Sernert N, Papadogiannakis N, Kartus J (2012) The reharvested patellar tendon has the potential for ligamentization when used for anterior cruciate ligament revision surgery. Knee Surg Sports Traumatol Arthrosc 20(6):1168–1174

54. Tohyama H, Yasuda K (2002) The effect of increased stress on the patellar tendon. J Bone Joint Surg Br 84(3):440–446

55. Unterhauser FN, Bosch U, Zeichen J, Weiler A (2004) Alpha-smooth muscle actin containing contractile fibroblastic cells in human knee arthrofibrosis tissue. Winner of the AGA-DonJoy Award 2003. Arch Orthop Trauma Surg 124(9):585–591

56. Unterhauser FN, Bail HJ, Hoher J, Haas NP, Weiler A (2003) Endoligamentous revascularization of an anterior cruciate ligament graft. Clin Orthop Relat Res (414):276–288

57. Vogrin M, Rupreht M, Dinevski D, Haspl M, Kuhta M, Jevsek M, Knezevic M, Rozman P (2010) Effects of a platelet gel on early graft revascularization after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind, clinical trial. Eur Surg Res 45(2):77–85

58. Weiler A, Peters G, Maurer J, Unterhauser FN, Sudkamp NP (2001) Biomechanical properties and vascularity of an anterior cruciate ligament graft can be predicted by contrast-enhanced magnetic resonance imaging. A two-year study in sheep. Am J Sports Med 29(6):751–761

59. Weiler A, Hoffmann RF, Bail HJ, Rehm O, Sudkamp NP (2002) Tendon healing in a bone tunnel. Part II: Histologic analysis after biodegradable interference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. Arthroscopy 18(2): 124–135

60. Weiler A, Unterhauser FN, Bail HJ, Huning M, Haas NP (2002) Alpha-smooth muscle actin is expressed by fibroblastic cells of the ovine anterior cruciate ligament and its free tendon graft during remodeling. J Orthop Res 20(2):310–317

61. Weiler A, Peine R, Pashmineh-Azar A, Abel C, Sudkamp NP, Hoffmann RF (2002) Tendon healing in a bone tunnel. Part I: Biomechanical results after biodegradable in terference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. Arthroscopy 18(2):113–123

62. Weiler A, Forster C, Hunt P, Falk R, Jung T, Unterhauser FN, Bergmann V, Schmidmaier G, Haas NP (2004) The influence of locally applied platelet-derived growth factor-BB on free tendon graft remodeling after anterior cruciate ligament reconstruction. Am J Sports Med 32(4):881–891

63. Xu Y, Ao YF (2009) Histological and biomechanical studies of inter-strand healing in four-strand autograft anterior cruciate ligament reconstruction in a rabbit model. Knee Surg Sports Traumatol Arthrosc 17(7):770–777

64. Yoshikawa T, Tohyama H, Katsura T, Kondo E, Kotani Y, Matsumoto H, Toyama Y, Yasuda K (2006) Effects of local administration of vascular endothelial growth factor on mechanical characteristics of the semitendinosus tendon graft after anterior cruciate ligament reconstruction in sheep. Am J Sports Med 34(12):1918–1925

65. Zaffagnini S, De Pasquale V, Marchesini Reggiani L, Russo A, Agati P, Bacchelli B, Marcacci M (2007) Neoligamentization process of BTPB used for ACL graft: histological evaluation from 6 months to 10 years. Knee 14(2):87–93

66. Zaffagnini S, De Pasquale V, Marchesini Reggiani L, Russo A, Agati P, Bacchelli B, Marcacci M (2010) Electron microscopy of the remodelling process in hamstring tendon used as ACL graft. Knee Surg Sports Traumatol Arthrosc 18(8):1052–1058

ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION WITH 4-STRAND HAMSTRING AUTOGRAFT AND ACCELERATED REHABILITATION: A 10-YEAR PROSPECTIVE STUDY ON CLINICAL RESULTS, KNEE OSTEOARTHRITIS AND ITS PREDICTORS

Rob P.A. Janssen, Arthur W.F. du Mée, Juliette van Valkenburg, Harm A.G.M. Sala, Carroll M. Tseng

Knee Surgery, Sports Traumatology, Arthroscopy 2013;21:1977–1988

Abstract

Purpose
Analysis of long-term clinical and radiological outcomes after anterior cruciate ligament (ACL) reconstruction with special attention to knee osteoarthritis and its predictors.

Methods
A prospective, consecutive case series of 100 patients. Arthroscopic transtibial ACL reconstruction was performed using 4-strand hamstring tendon autografts with a standardized accelerated rehabilitation protocol. Analysis was performed preoperatively and 10 years postoperatively. Clinical examination included Lysholm- and Tegner scores, IKDC (International Knee Documentation Committee) score, KT-1000 testing (MEDmetric Co., San Diego, CA, USA) and leg circumference measurements. Radiological evaluation included AP weight-bearing, lateral knee, Rosenberg and sky view X-rays. Radiological classifications were according to Ahlbäck and Kellgren&Lawrence. Statistical analysis included univariate and multivariate logistic regressions.

Results
Clinical outcome A significant improvement ($P < 0.001$) between preoperative and postoperative measurements could be demonstrated for the Lysholm- and Tegner scores, IKDC patient subjective assessment, KT-1000 measurements, pivot shift test, IKDC score and one-leg hop test. A pivot shift phenomenon (glide) was still present in 43 (50%) patients and correlated with lower levels of activity ($P < 0.022$).
Radiological outcome At follow-up, 46 (53.5%) patients had signs of osteoarthritis (OA). In this group, 33 patients (72%) had chondral lesions (≥ grade 2) at time of ACL reconstruction. A history of medial meniscectomy before or at time of ACL reconstruction increased the risk of knee OA 4 times (95% CI 1.41–11.5). An ICRS grade 3 at time of ACL reconstruction increased the risk of knee OA by 5.2 times (95% CI 1.09–24.8). Tegner score, pivot shift phenomenon and time interval from injury to ACL reconstruction were not significant predictors for radiographic signs of knee OA.

Conclusion
Transtibial ACL reconstruction with 4-strand hamstring autograft and accelerated rehabilitation restored anteroposterior knee stability. Clinical parameters and patient satisfaction improved significantly. At 10-year follow-up, radiological signs of OA were present in 53.5% of the subjects. Risk factors for OA were meniscectomy prior to, or at time of ACL reconstruction and chondral lesions at time of ACL reconstruction.

Keywords
Anterior cruciate ligament reconstruction · Hamstring autograft · Knee · Osteoarthritis · Accelerated rehabilitation · Long term · Radiological

Level of evidence II

Introduction

Injuries of the anterior cruciate ligament (ACL) frequently occur in cutting and pivoting sports such as football (soccer), field hockey, indoor sports, alpine skiing and tennis.[7, 11, 28, 48, 49] In Scandinavia, 40–50% of all ACL ruptures occur during football.[17] Women suffer ACL ruptures more frequently than men.[1] The overall incidence of ACL injury is 78 per 100.000 persons.[45] The group between 15 and 39 years old, which could be described as the group at risk, shows an incidence of 85–91 in 100.000 people per year.[17] Functional instability of the knee can be treated by ACL reconstruction, which ranks number 6 of most performed orthopaedic operations.[49] The popularity of hamstring autografts for ACL reconstructions is growing.[17, 49] The success rate varies between 55–95% depending on the surgical technique and the level of sports activity after reconstruction.[17, 32, 49]

There have been alarming reports on the increased risk of knee osteoarthritis (OA) in both ACL-deficient and ACL-reconstructed knees in the long term.[4, 16, 20, 29, 33, 35–37, 41–48, 51] The development of OA is multifactorial. Factors that might be of influence are the degree of initial trauma to the knee, inflammatory responses, additional or subsequent meniscal and chondral lesions, age, gender, genetics, range of motion, type of surgery, timing of ACL reconstruction and activity level after ACL reconstruction.[5, 6, 8–11, 14, 16, 18–21, 24, 27–29, 32, 33, 35, 36, 39–41, 44, 46–48, 50, 52–54]

Few reports have been presented on long-term results in terms of OA after ACL reconstruction with hamstring grafts.[22, 32, 39, 50] In the present study, the clinical and radiological long-term results (9–11 years) of ACL reconstruction with 4-strand hamstring autograft are presented.

Materials and methods

One hundred consecutive patients, scheduled for arthroscopic ACL reconstruction between August 1998 and June 2000, were included in the prospective study. All patients provided informed consent to participate in the study. The study was approved by an independent medical ethics committee.

Inclusion criteria were solitary anterior cruciate ligament deficiency with a positive pivot shift test; functional instability and arthroscopic ACL reconstruction with 4-strand hamstring autograft between August 1998 and June 2000. Exclusion criteria were additional knee ligament injuries; posterolateral insufficiency; history of fractures of the extremity and unwillingness to participate in the study.

To maximize the group attending the final follow-up, all patients received a written invitation. All patients could be traced and contacted. After a mean follow-up of 10 years, 88 patients had a complete follow-up with all primary outcome measurements provided. Reasons for lost to follow-up were emigration (n = 5), death not related to the knee condition (n = 1), psychiatric disorder (n = 2) and unwillingness to participate in the follow-up (n = 4). In this group of four patients, two reported a good knee function and could not be convinced to take part in the final follow-up. Two patients were unwilling to take part in the follow-up because of a disappointing experience in the past. These two patients did attend the regular follow-up after ACL reconstruction up to 1 year postoperatively and did not experience any complications with good knee stability according to KT-1000 measurements. Finally, 2 patients were excluded from the evaluation because there were no radiographs taken at the final follow-up due to pregnancy.

There were 86 patients in the final group (86%): 29 women (34%) and 57 men (66%). Baseline characteristics are presented in Table 1. The mean interval from injury to ACL reconstruction was 5 years (±4.8). The mean age at ACL reconstruction was 31.2 years (±8.0). The mean body mass index (BMI) at ACL reconstruction was 24.5 kg/m^2 (±3.1). The mean follow-up was 10 years (±0.7). At time of ACL reconstruction, 24 subjects (28%) had an ACL injury without meniscal injury, and 62 subjects (72%) had a history of meniscal injury or meniscectomy at the time of operation. Forty-five subjects (52%) had a medial meniscectomy, and 30 (35%) a lateral meniscectomy. Seven of these subjects (8%) had both medial and lateral meniscectomies. Eighteen subjects (21%) had no chondral lesions at the time of ACL reconstruction, 28 (33%) had chondral lesions ICRS grade 3. No grade 4 chondral lesion was detected. Two subjects had cartilage lesions that required debridement. All but six subjects had a history of preceding knee operations. In 4 cases, the operation was a revision operation after earlier reconstruction with bone-patellar tendon-bone autografts.

Surgical procedure
The ACL reconstructions were performed by the same senior orthopaedic surgeon (HS). The surgical technique for ACL reconstruction was identical in all patients: a transtibial technique with Bone Mulch Screw fixation on the femur and WasherLoc fixation on the tibia (surgical technique by S.M. Howell MD. Fixation materials by Arthrotec, Warsaw, IN, USA). The graft was a 4-strand semitendinosus/gracilis tendon. Tension on the hamstring autograft at the time of fixation was 90–100 N, with the knee in full extension.

Rehabilitation protocol
All patients enrolled in a standardized brace-free accelerated rehabilitation programme which has been described in previous publications.[25, 26]

Clinical and radiological outcome
Data collection was prospective. Prior to ACL reconstruction, an independent orthopaedic surgeon (RJ) performed the clinical examination. This included the Lysholm score, Tegner score, IKDC, KT-1000 arthrometer laxity testing (MEDmetric Co., San Diego, CA, USA), one-leg hop test and upper leg circumference of both legs as well as radiological evaluation. At time of ACL reconstruction, meniscal and cartilage status and any performed meniscal or cartilage treatment were documented. At final follow-up, all clinical and radiological measurements were repeated by the same independent orthopaedic surgeon (RJ). He was blinded for the self-reported patient data that was assessed and documented by an orthopaedic resident. He was also blinded for the radiological results at time of clinical evaluation.

Radiographs of both knees, including weight-bearing AP, 45 degree PA flexion weight-bearing (Rosenberg), lateral and sky views, were scored according to Ahlbäck and Kellgren&Lawrence classifications using the contralateral knee as reference.[3, 13, 14] The independent examiners, an orthopaedic surgeon (RJ) and a musculoskeletal radiologist (CT) were blinded. The interval between the first and the second assessment of the radiographs was 2 weeks. A combination of Ahlbäck grade I and Kellgren&Lawrence (K&L) grade 3 was defined as 'radiographic signs of knee OA'.

Statistical analysis
Results are presented as means and standard deviations (SD), medians (minimum and maximum) or odds ratios (OR) and 95% confidence intervals (CI) as appropriate. A paired t test or the Wilcoxon signed rank test was used to compare paired measurements of two different timeframes depending on parametric or nonparametric distribution of the data. To test for associations between nonparametric unpaired data, the Mann-Whitney U test was used if the outcome variable was nominal. If the outcome variable was categorical, a one-way ANOVA test with Bonferroni correction was used. To compare outcome between the osteoarthritis group and the non-osteoarthritis group, t test or the Mann-Whitney U test were used depending on parametric or nonparametric distribution of the data. The association between the two independent nonparametric variables pivot shift test and the Tegner score was also calculated with the Mann-Whitney U test. A univariate logistic regression analysis was performed to assess statistically significant predictors for knee OA. Biologically plausible interaction terms between the possible predictors were tested. A multivariate logistic regression model was made with the significant predictors of the outcome variable by the univariate logistic regression analysis. For the radiological analysis, Cohen's kappa values for inter-rater and intra-rater variability were calculated. Statistical significance was set at $P < 0.05$.

Results

The results for clinical outcome are summarized in Table 2. A significant improvement ($P < 0.001$) between preoperative and postoperative measurements was shown for the Lysholm score, Tegner score, IKDC patient subjective assessment, KT-1000 measurements, pivot shift test, IKDC score and one-leg hop test.

There was a significant correlation between the Tegner score and pivot shift phenomenon ($P = 0.022$). Subjects with grade 2 or 3 pivot shift had a median Tegner score of 2 grades lower compared to subjects with grade 0 or 1 pivot shift. No correlation could be demonstrated between the final Tegner score and BMI or the side-to-side difference as measured by the KT-1000 arthrometer.

Radiological assessment
Details of the radiological evaluation are given in Table 3. Radiographic signs of knee OA were shown in 46 (53.5%) patients at final follow-up. Thirty-three subjects (72%) had ICRS grade 2 or 3 chondral lesions at time of ACL reconstruction. Four out of 20 patients with an isolated ACL injury (20%) developed knee OA. In contrast, 40 out of 62 subjects (64.5%) with combined ACL and meniscal injury developed knee OA. Patients (n = 8) without any meniscal or cartilage injury had an OA rate of 12.5%. The kappa for intra-rater variability was 0.59 (P < 0.001). The kappa for inter-rater variability was 0.72 (P < 0.001).
Table 4 shows the main demographic characteristics and all pre- and postoperative measurements specified for the osteoarthritis group and the non-osteoarthritis group.

Univariate logistic regression analysis
Table 5 shows the results of the univariate logistic regression analysis. Four factors were predictors for the development of knee OA after ACL reconstruction. There were no interactions found between any of these four predictors.

1. Patient age at time of ACL reconstruction (odds ratio OR = 1.06; 95% CI 1.0-1.1). When transformed into a nominal variable, patients ≥ 30 years old had a 3.1 (95% CI 1.3-7.5) times higher risk of OA compared to patients < 30 years.
2. Cartilage status graded according to the ICRS classification at time of ACL reconstruction. Patients with grade 3 in any knee compartment at time of ACL reconstruction had a 9.5 (95% CI 2.4-37.5) times higher risk of OA than patients with grade 2. An OR for grade 4 compared to grade 3 could not be calculated because there were no patients with grade 4 at time of ACL reconstruction. The OR for grade 1 or 2 was not significant. When transformed into a nominal variable, patients with grade 2 or worse had a 5.8 (95% CI 2.2-15.0) times higher risk of knee OA than patients with grade 0 or 1. Patients with grade 3 had a 5.3 (95% CI 1.9-15.3) times higher risk than patients with grade 0-2.
3. History of medial meniscectomy increased the risk of knee OA by 5.1 (95% CI 2.0-13.2) compared to patients with no history of medial meniscectomy. Lateral meniscectomy was not a significant predictor in the study.
4. One-leg hop test performed preoperatively. Patients who scored grade D had a 12.3 (95% CI 1.4-109.1) times higher risk of knee OA than patients with grade C. When transformed into a nominal variable, patients with grade C or D had a 2.9 (1.2-7.1) times higher risk than patients with grade A or B.

The postoperatively measured Tegner score, pivot shift phenomenon and time interval from injury to ACL reconstruction were not significant predictors for radiographic signs of knee OA.

Multivariate logistic regression analysis
Included in the multivariate logistic regression analysis were patient age, status of the medial meniscus, status of the cartilage and one-leg hop test. These were all significant and noninteracting predictors in the univariate logistic regression analysis. In the multivariate logistic regression model, the status of the medial meniscus (OR = 4.0; 95% CI 1.4-11.5) and ICRS grade 3 chondral lesions at time of ACL reconstruction (OR = 5.2; 95% CI 1.1-24.8) remained significant predictors of knee OA.

Discussion

The most important finding of the present study is that transtibial ACL reconstruction with 4-strand hamstring autograft and accelerated rehabilitation restored anteroposterior knee stability with significant improvement of clinical parameters and patient satisfaction. At 10-year follow-up, radiological signs of OA were present in 53.5% of the subjects. The rate of OA after meniscectomy and ACL reconstruction was 64.5% in comparison to 20% in the group with isolated ACL reconstruction. Predictors for OA were patient age ≥ 30 years at time of ACL reconstruction, cartilage status ≥ ICRS grade 2 at time of ACL reconstruction, history of medial meniscectomy and preoperative one-leg hop test C and D. Multivariate logistic regression analysis showed the status of the medial meniscus and ICRS grade 3 cartilage condition at time of ACL reconstruction to be significant predictors for knee OA.

The rate of radiographic knee OA in an ACL-deficient knee has been described in several long-term studies.
Gillquist et al.[16] found 70% OA (10- to 20-year follow-up; Albäck I and II), Segawa et al.[51] 63% OA (12 years after ACL rupture). Main risks were meniscectomy, increased age at time of lesion, increased sports level, obesity and OA of the contralateral knee. Modification of sports activity level was the most important factor to avoid the combined injury of meniscus and osteoarthritis.[51] The results for meniscectomy and increased age at time of injury were comparable to the results of the present study. However, no significant relation was found between the level of sports activity as measured by Tegner score and OA.

Lohmander et al.[35] described 51% OA (≥ K&L grade 2), pain and functional limitations in female football (soccer) players, 12 years after ACL rupture.
Nebelung et al.[42] found 95% meniscal and cartilage damage at 35-year follow-up of Olympic and high-level athletes with ACL-deficient knees. Total knee replacement had been performed in 53% of the subjects.[42]
In contrast, Neuman et al.[43] found only 16% OA, 15 years after ACL rupture. Their patients had been advised against pivoting sports. Meniscectomy was the primary risk factor for knee OA. In contrast to the present study, they did not find a correlation between osteochondral injury diagnosed at primary surgery after ACL injury and OA.[43]
Øiestad et al.[46] concluded in a review that it is difficult to compare various studies on long-term knee OA after ACL rupture due to the lack of a universal radiologic classification.

Studies on long-term knee OA after ACL reconstruction have shown various results.
Daniel et al.[12] prospectively compared ACL reconstruction and conservative treatment after ACL rupture. Reconstructed patients had a higher level of OA detected by radiograph and bone scan.[12]
Kessler et al.[29] found 42% OA after ACL reconstruction, 25% after conservative treatment (K&L grade 2, follow-up 11 years). The authors postulated that ACL surgery is a new trauma to the knee prolonging the already present inflammatory response after ACL rupture.[12, 29] Hart et al.[20] analysed bone-patellar tendon-bone ACL reconstructions with single-photon emission computed tomography. At 10 years, they only found 7% OA with a significant increase in degenerative changes in patients with combined ACL and meniscal injury.[20]
Aït Si Selmi et al.[4] reported 37.2% joint space narrowing (JSN) on radiographs, 17 years after ACL reconstruction. Knees with a preserved (healthy or sutured) medial meniscus had a better radiological outcome. Medial meniscectomy, residual laxity, and femoral chondral defects were associated with OA.[4]
The present study also showed both medial meniscectomy and chondral lesions ≥ grade 3 as significant predictors of OA. However, there was no relationship between OA and residual laxity or pivot shift after ACL reconstruction. In contrast to Lebel et al.[31] and Kessler et al.[29], the present study did not show an association between the patient's BMI and OA.

The association between radiographic severity and knee symptoms as well as function was investigated by Øiestad et al.[47] Patients with severe OA had increased symptoms and impairment of function compared to patients without OA.[47]

Shelbourne et al.[52] described the importance of knee function after ACL reconstruction in relation to OA. They found less OA in patients who achieved and maintained normal function, regardless of the status of the meniscus.[52] In the present study, no correlation was found between range of motion and OA.

Struewer et al.[54] described 74.2% OA after bone-patellar tendon-bone ACL reconstruction (K&L grade ≥ 2, follow-up 13.5 years). In a randomised trial, Sajovic et al. found a higher prevalence of OA after ACL reconstruction with bone-patellar tendon-bone grafts compared to hamstring tendon grafts (84% versus 63%, follow-up 11 years).[50]
Mascarenhas et al.[38] compared the two techniques in young athletes. Hamstring ACL reconstruction led to better preservation of extension, higher patient-reported outcomes and less OA than patellar tendon ACL reconstruction.[38] Comparable results were shown by Leys et al.[32]
In contrast, other authors found no difference in knee OA after ACL reconstruction with hamstring autograft versus bone-patellar tendon-bone autograft.[2, 22, 34]

The rate of OA after ACL reconstruction is comparable to long-term ACL-deficient knees.[11, 18, 31-38] The incidence of 53,5% OA (Ahlbäck I and K&L grade 3) after hamstring tendon ACL reconstruction in the present study is comparable to previous research. Both status of the medial meniscus and cartilage condition ICRS grade ≥ 3 were significant predictors of OA.

All aforementioned studies have also shown that meniscectomy is a significant independent risk factor for knee OA. Andersson-Molina et al.[5] have demonstrated that the amount of resected meniscus is directly related to the rate of OA. Neyret et al.[44] reported that an isolated medial meniscectomy without ACL injury leads to an OA rate of 90% at 20-year follow-up. Øiestad et al.[48] compared the prevalence of radiographic and symptomatic knee OA after ACL reconstruction between subjects with isolated ACL injuries and those with combined ACL and meniscal and/or chondral lesions. A significantly higher prevalence of OA occurred in patients with combined injuries (46% versus 32%).[48] Hui et al.[23] have examined 15-year follow-up after bone-patellar tendon-bone ACL reconstruction. They excluded patients with associated ligamentous injury requiring surgery, previous meniscectomy, or meniscal injury requiring more than one-third meniscectomy, chondral injury as well as an abnormal contralateral knee. The incidence of OA was still 51%.[23]

The differences in study design, radiological definition of OA and OA classifications may lead to a wide range of OA rates.[46] In their systematic review on knee OA after ACL injury, Øiestad et al.[46] concluded that previous reported prevalence of knee OA have been too high and recommended a list of criteria for future research on OA after ACL reconstruction.
The present study fulfills all these criteria. In the cohort of 86 subjects, 53.5% had radiographic signs of OA (K&L grade 3) at 10-year follow-up, 73.3% was graded K&L grade 2 or worse.

Which factors could have influenced the high rate of knee OA after hamstring tendon ACL reconstruction?
The present study considered radiographic signs of knee OA to be present with JSN. Radiological evaluation was done by weight-bearing AP, lateral and skyline views as well as the Rosenberg view. The Rosenberg view is more accurate, more specific and more sensitive than conventional weight-bearing anteroposterior radiographs in detecting early JSN.[13, 15] This will result in higher OA percentages compared to studies that did not incorporate this view.

Another variable might be the time interval between the injury and ACL reconstruction. In the present study, this interval was 5 years (±4.8). This may be related to the number of meniscectomies performed prior to ACL reconstruction.

Patient age might have been of influence as well. The group with knee OA was 4 years older than the non-osteoarthritis group and had an initial cartilage status that was two ICRS grades worse compared to the non-osteoarthritis group. The univariate regression analysis confirmed a relationship between the patient's age at ACL reconstruction and OA. However, in the multivariate regression model, the patient's age at ACL reconstruction did not prove to be a significant predictor of OA. This could be explained by selection bias. It is possible that there was more reluctance to surgery in older patients.

A second limitation of the present study is the lost to follow-up of 12 patients. Although there were no significant differences in gender or age between the study participants and those lost to follow-up, it might have biased the results.

Another limitation of the present study is the high number of meniscectomies. Most patients were referred to our centre for ACL reconstruction after arthroscopic meniscectomy was performed at other institutions. Meniscus repair occurred in < 5% of patients in The Netherlands during those years. This projects on the rate of OA in the present study.

The ACL reconstruction technique used in the present study is nowadays recognized as a nonanatomic reconstruction.[30] The influence of anatomy of reconstruction in the present study could not be analysed due to the lack of long-term evidence of prevention of OA after anatomic ACL reconstruction.

Another limitation of the present study is the limited number of lateral meniscectomies in the study group. Lateral meniscectomy might have been a predictor of knee OA in a larger study population.

The clinical relevance of the study is that patients may be informed that ACL reconstruction does not prevent long-term knee OA.

Conclusion

Transtibial ACL reconstruction with 4-strand hamstring autograft and accelerated rehabilitation restored anteroposterior knee stability. Clinical parameters and patient satisfaction improved significantly. At 10-year follow-up, radiological signs of OA were present in 53.5% of the subjects. Risk factors for OA were meniscectomy prior to or at time of ACL reconstruction and chondral lesions at time of ACL reconstruction.

Table 1 Patient baseline characteristics

	n	%
Trauma mechanism		
Non-contact trauma	54	62.8
Contact trauma	12	14.0
Non-trauma, graduate	8	9.3
Non-trauma, sudden	5	5.8
Not specified	7	8.1
Activity at injury		
Sports	69	80.2
Work	5	5.8
Traffic	3	3.5
ADL	2	2.3
Not specified	7	8.1
Chief complaint		
Giving way	83	96.5
Pain	1	1.2
Locking	1	1.2
Not specified	1	1.2
Leg alignment		
Straight	75	87.2
Varus	7	8.1
Valgus	2	2.3
Not specified	2	2.3
Body mass index (kg/m^2)		
Normal (<25)	45	52.3
Overweight (25-30)	33	38.4
Obese (≥30)	4	4.7
Not specified	4	4.7
Previous operations		
Number of previous knee operations		
0	6	7.0
1	49	57.0
2	18	20.9
3	9	10.5
>3	2	2.3
Not specified	2	2.3
Subjects with previous ACL reconstruction	4	4.7
Chondral lesions at ACL reconstruction		
Grade 0	18	20.9
Grade 1	18	20.9
Grade 2	18	20.9
Grade 3	28	32.6
Grade 4	0	0.0
Not specified	4	4.7
Meniscectomy		
Subjects with meniscectomy before or during ACL reconstruction	62	72.1
Medial lesions	45	52.3
Lateral lesions	30	34.9

n number

Table 2 Summary of clinical outcome

Measurements: preoperative vs. 10 years postoperative														
	Score or grade*		**Number of subjects (%) per grade**											***P***
Age at ACL reconstruction (years)	31.2	(±8.0)												
Time to ACL reconstruction (years)	4.9	(±4.8)												
BMI at ACL reconstruction (kg/m^2)	24.5	(±3.1)												
ICRS grade			Grade 0		Grade 1		Grade 2		Grade 3		Not specified			
All compartments	2	(0–3)	18	(20.9 %)	18	(20.9 %)	18	(20.9 %)	28	(32.6 %)	4	(4.7 %)		
Tibiofemoral	2	(0–3)	20	(23.3 %)	19	(22.1 %)	18	(20.9 %)	25	(29.1 %)	4	(4.7 %)		
Patellofemoral	1	(0–3)	40	(46.5 %)	31	(36.0 %)	6	(7.0 %)	5	(5.8 %)	4	(4.7 %)		
Lysholm score														
Preoperative	68	(31-95)												<0.001
Postoperative	95	(34-100)												
Tegner score														
Preoperative	3	(0–6)												<0.001
Postoperative	6	(2–9)												
IKDC subjective score			Grade A		Grade B		Grade C		Grade D		Not specified			
Preoperative	3	(2–4) ‘‘grade C’’	4	(4.7 %)	68	(79.1 %)	14	(16.3 %)	0	(0.0 %)				<0.001
Postoperative	2	(1–3) ‘‘grade B’’	24	(27.9 %)	53	(61.6 %)	7	(8.1 %)	0	(0.0 %)	2	(2.3 %)		
KT-1000 (133 N) SSD (mm)			0–2		3–5		[5				Not specified			
Preoperative	7.9	(±3.1)	0	(0 %)	16	(19.3 %)	66	(79.5 %)			1	(1.2 %)		<0.001
Postoperative	2.3	(±2.9)	37	(52.1 %)	20	(28.2 %)	14	(19.7 %)						
Pivot shift test grade			No pivot		Glide (+)		Click (++)		Clunk (+++)					
Preoperative	3	(1–3) ‘‘Clunk’’	0	(0 %)	1	(1.2 %)	20	(23.2 %)	65	(75.6 %)				<0.001
Postoperative	1	(0–3) ‘‘Glide’’	43	(50 %)	28	(32.6 %)	13	(15.1 %)	2	(2.3 %)				
IKDC score, ligament examination			Grade A		Grade B		Grade C		Grade D					
Preoperative	4	(1–4) ‘‘grade D’’	2	(2.3)	0	(0 %)	14	(16.3)	70	(81.4)				<0.001
Postoperative	2	(1–4) ‘‘grade B’’	20	(23.3)	45	(52.3 %)	18	(20.9 %)	3	(3.5 %)				
Quadriceps circumference SSD (cm)														
Preoperative	0.0	(-4.0-4.0)												n.s.
Postoperative	0.0	(-5.0-3.0)												
Calf circumference SSD (cm)														
Preoperative	0.00	(-2.5-3.0)												n.s.
Postoperative	0.00	(-3.0-3.0)												
Range of motion			Grade A		Grade B		Grade C		Grade D					
Preoperative	1	(1–3)	81	(94.2 %)	4	(4.7 %)	1	(1.2 %)	0	(0.0 %)				n.s.
Postoperative	1	(1–4)	78	(90.7 %)	6	(7.0 %)	1	(1.2 %)	1	(1.2 %)				
One-leg hop test grade			Grade A (100-90 %)		Grade B (89-76 %)		Grade C (75-50 %)		Grade D (<50 %)		Not specified			
Preoperative	2	(1–4) ‘‘grade B’’	29	(33.7 %)	16	(18.6 %)	28	(32.6 %)	11	(12.8 %)	2	(2.3 %)		<0.001
Postoperative	1	(1–3) ‘‘grade A’’	57	(66.3 %)	22	(25.6 %)	6	(7.0 %)	0	(0.0 %)	1	(1.2 %)		
IKDC score			Grade A		Grade B		Grade C		Grade D					
Preoperative	4	(3–4) ‘‘grade D’’	0	(0 %)	0	(0 %)	14	(16.3 %)	72	(83.7 %)				<0.001
Postoperative	2	(1–4) ‘‘grade B’’	4	(4.7 %)	49	(57.0 %)	29	(33.7 %)	4	(4.7 %)				

* In this column, values are provided as means (±SD) or as medians (minimum-maximum)
SSD Side to Side Difference
n.s. non-significant

Table 3 Radiological evaluation

Ahlbäck classification					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
36 (41.9 %)	46 (53.5 %)	3 (3.5 %)	1 (1.2 %)	0 (0.0 %)	0 (0.0 %)
Kellgren & Lawrence classification					
Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
7 (8.1 %)	16 (18.6 %)	17 (19.8 %)	41 (47.7 %)	5 (5.8 %)	

Table 4

Main demographic characteristics and all pre- and postoperative measurements specified for the osteoarthritis group and the non-osteoarthritis group

	Osteoarthritis		**No osteoarthritis**		
	score or grade*		**score or grade***		***P***
Cases per group *(n)*	46	(100.0 %)	40	(100.0 %)	
Male gender *(n)*	32	(69.6 %)	25	(62.5 %)	n.s.
Age at ACL reconstruction (years)	33.1	(± 8.4)	29.3	(± 8.1)	0.04
Time to ACL reconstruction (years)	5.5	(± 4.7)	4.3	(± 4.9)	n.s.
BMI at ACL reconstruction (kg/m²)	25.05	(± 3.3)	23.9	(± 2.9)	n.s.
ICRS grade					
All compartments	3	(0-3)	1	(0–3)	<0.001
Tibiofemoral	2.5	(0-3)	1	(0–3)	<0.001
Patellofemoral	0	(0-3)	0	(0–3)	n.s.
History of meniscectomy *(n)*	40	(90.9 %)	22	(55.0 %)	
Lysholm score					
Preoperative	70	(43-95)	67	(31-90)	n.s.
Postoperative	93	(34-100)	96	(57-100)	n.s.
Tegner score					
Preoperative	3	(0-6)	3	(0–6)	n.s.
Postoperative	6	(3-9)	6	(2–9)	n.s.
IKDC subjective score					
Preoperative	3	(2-4) ''grade C''	3	(2–4) ''grade C''	n.s.
Postoperative	2	(1-3) ''grade B''	2	(1–3) ''grade B''	0.004
KT-1000 (133 N) SSD (mm)					
Preoperative	8.2	(± 3.2)	8.0	(± 2.9)	n.s.
Postoperative	1.5	(± 3.1)	2.9	(± 2.9)	n.s.
Pivot shift test grade					
Preoperative	3	(1-3) ''Clunk (+++)''	3	(2–3) ''Clunk (+++)''	n.s.
Postoperative	0	(0-2) ''no pivot''	1	(0–3) ''Glide (+)''	n.s.
IKDC score, ligament examination					
Preoperative	4	(1-4) ''grade D''	4	(1–4) ''grade D''	n.s.
Postoperative	2	(1-4) ''grade B''	2	(1–4) ''grade B''	n.s.
Quadriceps circumference SSD (cm)					
Preoperative	0	(-2-3)	0	(-4–4)	n.s.
Postoperative	0	(-5-3)	0	(-2–2)	n.s.
Calf circumference SSD (cm)					
Preoperative	0	(-2-3)	0	(-2.5–2)	n.s.
Postoperative	0	(-2-3)	0	(-3–3)	n.s.
Range of motion					
Preoperative	1	(1-2)	1	(1–3)	n.s.
Postoperative	1	(1-2)	1	(1–2)	n.s.
One-leg hop test grade					
Preoperative	3	(1-4) ''grade C''	2	(1–4) ''grade B''	0.03
Postoperative	1	(1-3) ''grade A''	1	(1–2) ''grade A''	0.02
IKDC score					
Preoperative	4	(3-4) ''grade D''	4	(3–4) ''grade D''	n.s.
Postoperative	2	(1-4) ''grade B''	2	(1–4) ''grade B''	n.s.

* Values are provided as: number (%), means (± SD), medians (minimum-maximum)

SSD Side to Side Difference

n number, *n.s.* non-significant

Table 5

Results of the univariate logistic regression analysis for predictors of knee OA

	Odds ratio	95 % CI	*P*
Demographic factors			
Gender	0.73	0.30–1.79	n.s.
Time to ACL reconstruction	1.06	0.96–1.17	n.s.
Age at ACL reconstruction	1.06	1.01–1.12	0.04
Age ≥ 30 years at ACL reconstruction	3.10	1.28–7.50	0.01
Body mass index	1.15	0.99–1.33	n.s.
Complications	1.55	0.60–3.96	n.s.
Preoperative measurements			
Lysholm score	1.01	0.98–1.04	n.s.
Tegner score	1.03	0.74–1.54	n.s.
IKDC subjective grade	1.01	0.98–1.05	n.s.
Leg circumference			
Quadriceps circumference SSD	1.24	0.90–1.71	n.s.
Calf circumference SSD	1.28	0.81–2.01	n.s.
Range of motion (A–D)			
Grade A	1.00		
Grade B	–	–	–
Grade C	2.65	0.27–26.6	n.s.
Grade D	0.00	0.00–0.00	n.s.
One-leg hop test (A–D)			
Grade A	1.00		
Grade B	0.74	0.21–2.58	n.s.
Grade C	1.42	0.50–4.03	n.s.
Grade D	12.31	1.39–109.1	0.02
Grade C or worse	2.89	1.18–7.08	0.02
IKDC grade (A–D)			
Grade A	1.00		
Grade B	–	–	–
Grade C	–	–	–
Grade D	1.18	0.38–3.72	n.s.
Peroperative findings			
ICRS grade (0–4)			
ICRS grade 0	1.00		
ICRS grade 1	1.30	0.31–5.39	n.s.
ICRS grade 2	4.09	1.01–16.58	0.05
ICRS grade 3	9.53	2.42–37.54	<0.001
ICRS grade 4	–	–	–
Grade 2 or worse	5.77	2.22–15.01	<0.001
Grade 3 or worse	5.33	1.86–15.29	0.002
Meniscectomy			
Medial meniscectomy prior to or during ACL reconstruction	5.13	2.0–13.17	<0.001
Lateral meniscectomy prior to or during ACL reconstruction	0.86	0.92–5.94	n.s.

SSD Side to Side Difference
n.s. non-significant

References

1. Ageberg E, Forssblad M, Herbertsson P, Roos EM (2010) Sex differences in patient-reported outcomes after anterior cruciate ligament reconstruction: data from the Swedish knee ligament register. Am J Sports Med 38(7):1334–1342

2. Aglietti P, Giron F, Buzzi R, Biddau F, Sasso F (2004) Anterior cruciate ligament reconstruction: bone–patellar tendon–bone compared with double semitendinosus and gracilis tendon grafts. A prospective, randomized clinical trial. J Bone Joint Surg Am (10):2143–2155

3. Ahlback S (1968) Osteoarthrosis of the knee. A radiographic investigation. Acta Radiol Diagn (Stockh):Suppl 277:277–272

4. Ait Si Selmi T, Fithian D, Neyret P (2006) The evolution of osteoarthritis in 103 patients with ACL reconstruction at 17 years follow-up. Knee 13(5):353–358

5. Andersson-Molina H, Karlsson H, Rockborn P (2002) Arthroscopic partial and total meniscectomy: A long-term follow-up study with matched controls. Arthroscopy 18(2):183–189

6. Ayeni OR, Chahal M, Tran MN, Sprague S (2012) Pivot shift as an outcome measure for ACL reconstruction: a systematic review. Knee Surg Sports Traumatol Arthrosc 20(4):767–777

7. Bahr R, Holme I (2003) Risk factors for sports injuries–a methodological approach. Br J Sports Med 37(5):384–392

8. Barber-Westin SD, Noyes FR (2011) Factors used to determine return to unrestricted sports activities after anterior cruciate ligament reconstruction. Arthroscopy 27(12):1697–1705

9. Beynnon BD, Johnson RJ, Naud S, Fleming BC, Abate JA, Brattbakk B, Nichols CE (2011) Accelerated versus nonaccelerated rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind investigation evaluating knee joint laxity using roentgen stereophotogrammetric analysis. Am J Sports Med 39(12):2536–2548

10. Borchers JR, Kaeding CC, Pedroza AD, Huston LJ, Spindler KP, Wright RW, Consortium M, the MG (2011) Intra-articular findings in primary and revision anterior cruciate ligament reconstruction surgery: a comparison of the MOON and MARS study groups. Am J Sports Med 39(9):1889–1893

11. Cohen M, Amaro JT, Ejnisman B, Carvalho RT, Nakano KK, Peccin MS, Teixeira R, Laurino CF, Abdalla RJ (2007) Anterior cruciate ligament reconstruction after 10 to 15 years: association between meniscectomy and osteoarthrosis. Arthroscopy 23(6): 629–634

12. Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR (1994) Fate of the ACL-injured patient. A prospective outcome study. Am J Sports Med 22(5): 632–644

13. Dervin GF, Feibel RJ, Rody K, Grabowski J (2001) 3-Foot standing AP versus 45 degrees PA radiograph for osteoarthritis of the knee. Clin J Sport Med 11(1):10–16

14. Fink C, Hoser C, Hackl W, Navarro RA, Benedetto KP (2001) Long-term outcome of operative or nonoperative treatment of anterior cruciate ligament rupture–is sports activity a determining variable? Int J Sports Med 22(4):304–309

15. Fontboté C, Nemtala F, Contreras O, Guerrero R (2008) Rosenberg projection for the radiological diagnosis of gonarthrosis. Rev Med Chile 136:880–884

16. Gillquist J, Messner K (1999) Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. Sports Med 27(3):143–156

17. Granan LP, Forssblad M, Lind M, Engebretsen L (2009) The Scandinavian ACL registries 2004–2007: baseline epidemiology. Acta Orthop 80(5):563–567

18. Hambly K, Griva K (2010) IKDC or KOOS: which one captures symptoms and disabilities most important to patients who have undergone initial anterior cruciate ligament reconstruction? Am J Sports Med 38(7):1395–1404

19. Hanypsiak BT, Spindler KP, Rothrock CR, Calabrese GJ, Richmond B, Herrenbruck TM, Parker RD (2008) Twelve-year follow-up on anterior cruciate ligament reconstruction: long-term outcomes of prospectively studied osseous and articular injuries. Am J Sports Med 36(4):671–677

20. Hart AJ, Buscombe J, Malone A, Dowd GS (2005) Assessment of osteoarthritis after reconstruction of the anterior cruciate ligament: a study using single-photon emission computed tomography at ten years. J Bone Joint Surg Br 87(11):1483–1487

21. Hoffelner T, Resch H, Moroder P, Atzwanger J, Wiplinger M, Hitzl W, Tauber M (2012) No increased occurrence of osteoarthritis after anterior cruciate ligament reconstruction after isolated anterior cruciate ligament injury in athletes. Arthroscopy 28(4):517–525

22. Holm I, Oiestad BE, Risberg MA, Aune AK (2010) No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up. Am J Sports Med 38(3):448–454

23. Hui C, Salmon LJ, Kok A, Maeno S, Linklater J, Pinczewski LA (2011) Fifteen-year outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft for "isolated" anterior cruciate ligament tear. Am J Sports Med 39(1):89–98

24. Isberg J, Faxen E, Laxdal G, Eriksson BI, Karrholm J, Karlsson J (2011) Will early reconstruction prevent abnormal kinematics after ACL injury? Two-year follow-up using dynamic radiostereometry in 14 patients operated with hamstring autografts. Knee Surg Sports Traumatol Arthrosc 19(10):1634–1642

25. Janssen RP, Velden van der MJ, Pasmans HL, Sala HA (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21(4):898–905

26. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299–1306

27. Jonsson H, Riklund-Ahlstrom K, Lind J (2004) Positive pivot shift after ACL reconstruction predicts later osteoarthrosis: 63 patients followed 5–9 years after surgery. Acta Orthop Scand 75(5):594–599

28. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC (2010) Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. Am J Sports Med 38(3):455–463

29. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS (2008) Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. Knee Surg Sports Traumatol Arthrosc 16(5):442–448

30. Kondo E, Merican AM, Yasuda K, Amis AA (2011) Biomechanical comparison of anatomic double-bundle, anatomic single-bundle, and nonanatomic single-bundle anterior cruciate ligament reconstructions. Am J Sports Med 39(2):279–288

31. Lebel B, Hulet C, Galaud B, Burdin G, Locker B, Vielpeau C (2008) Arthroscopic reconstruction of the anterior cruciate ligament using bone–patellar tendon–bone autograft: a minimum 10-year follow-up. Am J Sports Med 36(7):1275–1282

32. Leys T, Salmon L, Waller A, Linklater J, Pinczewski L (2012) Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts. Am J Sports Med 40(3):595–605

33. Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ (2011) Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. Am J Sports Med 39(12):2595–2603

34. Liden M, Sernert N, Rostgard-Christensen L, Kartus C, Ejerhed L (2008) Osteoarthritic changes after anterior cruciate ligament reconstruction using bone–patellar tendon–bone or hamstring tendon autografts: a retrospective, 7-year radiographic and clinical follow-up study. Arthroscopy 24(8):899–908

35. Lohmander LS, Ostenberg A, Englund M, Roos H (2004) High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 50(10):3145–3152

36. Lohmander LS, Englund PM, Dahl LL, Roos EM (2007) The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 35(10):1756–1769

37. Maletius W, Messner K (1999) Eighteen- to twenty-four-year follow-up after com plete rupture of the anterior cruciate ligament. Am J Sports Med 27(6):711–717

38. Mascarenhas R, Tranovich MJ, Kropf EJ, Fu FH, Harner CD (2012) Bone–patellar tendon–bone autograft versus hamstring autograft anterior cruciate ligament reconstruction in the young athlete: a retrospective matched analysis with 2–10 year follow-up. Knee Surg Sports Traumatol Arthrosc 20(8):1520–1527

39. Meystre JL, Vallotton J, Benvenuti JF (1998) Double semitendinosus anterior cruciate ligament reconstruction: 10-year results. Knee Surg Sports Traumatol Arthrosc 6(2):76–81

40. Mohtadi NG, Chan DS, Dainty KN, Whelan DB (2011) Patellar tendon versus hamstring tendon autograft for anterior cruciate ligament rupture in adults. Cochrane Database Syst Rev(9):CD005960

41. Murray JR, Lindh AM, Hogan NA, Trezies AJ, Hutchinson JW, Parish E, Read JW, Cross MV (2012) Does anterior cruciate ligament reconstruction lead to degenerative disease?: Thirteen-year results after bone-patellar tendon-bone autograft. Am J Sports Med 40(2):404-413

42. Nebelung W, Wuschech H (2005) Thirty-five years of follow-up of anterior cruciate ligament-deficient knees in high-level athletes. Arthroscopy 21(6):696-702

43. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE (2008) Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. Am J Sports Med 36(9):1717-1725

44. Neyret P, Donell ST, Dejour H (1993) Results of partial meniscectomy related to the state of the anterior cruciate ligament. Review at 20 to 35 years. J Bone Joint Surg Br 75(1):36-40

45. Nordenvall R, Bahmanyar S, Adami J, Stenros C, Wredmark T, Fellander-Tsai L (2012) A population-based nationwide study of cruciate ligament injury in Sweden, 2001-2009: incidence, treatment, and sex differences. Am J Sports Med 40(8):1808-1813

46. Oiestad BE, Engebretsen L, Storheim K, Risberg MA (2009) Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med 37(7): 1434-1443

47. Oiestad BE, Holm I, Engebretsen L, Risberg MA (2011) The association between radiographic knee osteoarthritis and knee symptoms, function and quality of life 10-15 years after anterior cruciate ligament reconstruction. Br J Sports Med 45(7):583-588

48. Oiestad BE, Holm I, Aune AK, Gunderson R, Myklebust G, Engebretsen L, Fosdahl MA, Risberg MA (2010) Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction: a prospective study with 10 to 15 years of follow-up. Am J Sports Med 38(11):2201-2210

49. Prodromos CC (2008) The Anterior Cruciate Ligament. Reconstruction and Basic Science 1st ed. Saunders, an imprint of Elsevier, Inc.

50. Sajovic M, Strahovnik A, Dernovsek MZ, Skaza K (2011) Quality of life and clinical outcome comparison of semitendinosus and gracilis tendon versus patellar tendon autografts for anterior cruciate ligament reconstruction: an 11-year follow-up of a randomized controlled trial. Am J Sports Med 39(10):2161-2169

51. Segawa H, Omori G, Koga Y (2001) Long-term results of non-operative treatment of anterior cruciate ligament injury. Knee 8(1):5-11

52. Shelbourne KD, Urch SE, Gray T, Freeman H (2012) Loss of normal knee motion after anterior cruciate ligament reconstruction is associated with radiographic arthritic changes after surgery. Am J Sports Med 40(1):108-113

53. Stener S, Ejerhed L, Sernert N, Laxdal G, Rostgard-Christensen L, Kartus J (2010) A long-term, prospective, randomized study comparing biodegradable and metal interference screws in anterior cruciate ligament reconstruction surgery: radiographic results and clinical outcome. Am J Sports Med 38(8):1598-1605

54. Struewer J, Frangen TM, Ishaque B, Bliemel C, Efe T, Ruchholtz S, Ziring E (2012) Knee function and prevalence of osteoarthritis after isolated anterior cruciate ligament reconstruction using bone-patellar tendon-bone graft: long-term follow-up. Int Orthop 36(1):171-177

8

GENERAL DISCUSSION

This thesis presents novel insights into ACL reconstruction with hamstring tendon autograft and accelerated brace-free rehabilitation. The main findings and limitations of the studies have been discussed in the previous chapters. The general discussion will focus on the current perspective on accelerated rehabilitation after ACL reconstruction. The standardized accelerated brace-free rehabilitation protocol used in all studies of this thesis will be evaluated and recommendations made for rehabilitation and return to sports after hamstring tendon ACL reconstruction. A new model for ACL graft remodelling research will be presented. The clinical implications of this thesis will finalize the chapter.

Accelerated brace-free rehabilitation after ACL reconstruction revisited

In order to better understand the current perspective on accelerated rehabilitation, it is necessary to review the historical background of ACL rehabilitation. During the 1980's, former basic animal research led to the belief that intra-articular patellar tendon graft healing was a long-term process and included a phase in which the graft was partially necrotic and therefore needed protection.[34, 43, 82, 140] This protection included limited weight-bearing, restricted range of motion (ROM) and avoidance of early full terminal extension to prevent excessive stress on the reconstructed graft.[34] It also required wearing a knee brace as well as a delay in return to activities in daily living (ADL) and sports. Despite good ligamentous stability, common rehabilitation problems occurred including knee stiffness, lack of full extension, anterior knee pain, muscle weakness and knee crepitus.[34, 152]

Shelbourne et al. noticed that noncompliant patients, achieving full ROM, normal gait and resuming normal ADL earlier than prescribed, achieved faster return of strength and a quicker return to activities without graft failure.[152] Owing to the unexpected results, Shelbourne&Nitz decided to shift the focus of their rehabilitation in the 1990's to include: (1) obtaining full ROM preoperatively; (2) staying down postoperatively with elevation of the reconstructed knee; (3) using a cold compression device before and after surgery; (4) fully extending the knee on the day of surgery and maintaining full extension for the remainder of the postoperative period and; (5) flexing the knee past 90° on the day of surgery.[52, 149, 152] Based on the patient noncompliance, the use of crutches, splints and braces was no longer emphasized. These evolutionary changes became the basis of current accelerated brace-free rehabilitation protocols with a progressive scheme that allows patients to advance as they achieve quantifiable goals.[73, 74, 96, 97, 118, 152, 153, 165, 171, 175]

This thesis has shown that several factors need to be considered when accelerated brace-free rehabilitation after ACL reconstruction with hamstring tendons is prescribed.[43]
First, hamstring tendon autografts require fixation of soft tissue (tendon) to bone.[113] A period of 8-12 weeks is necessary for proper incorporation of hamstring tendon grafts in the bone tunnels.[43] Fixation of this soft tissue graft is considered the weak link early on after ACL reconstruction.[43, 61] Secure graft fixation during early rehabilitation and ADL improves graft-bone tunnel integration.[61]

Second, the intra-articular remodelling of the ACL hamstring tendon autograft requires an optimal balance between muscular strengthening exercises and loading of the graft, to stimulate graft cells to produce cellular and extracellular components for preservation of graft stability, without compromising graft integrity, which might result into an early stretch-out of the ACL reconstruction.[21, 23, 82, 140, 168]

Finally, early after ACL reconstruction, relative protection of the autograft donor site must be considered. Therefore, force generation from the hamstrings should be minimized when a hamstring tendon autograft is employed.[43]
In summary, accelerated brace-free rehabilitation needs to be as aggressive as possible in restoring function while still maintaining an optimal tissue healing environment.[118]

Rehabilitation after ACL reconstruction could be described as adaptations made to a complex biological system, founded on Kelso's dynamic patterns theory.[25, 91] This theory encompasses a total structure of complex systems and the consequences for the systems' behaviour.[91] Scientific evidence in rehabilitation research is frequently categorized in specific components, such as strengthening and neuromuscular programmes. This may lead to the danger of reductionism. For centuries, reductionism has been the subject of much discussion among scientists and philosophers, and has come to be an integral part of modern science.

The history of reductionism versus holistic approaches to scientific research has been described by Andersen.[6] In its strongest form, the world may be seen as a series of reductive levels: social groups, multicellular living things, cells, molecules, atoms, and finally as the smallest parts, the elementary particles. In contrast, holism, in the form of systems theories, builds on the idea that systemic relations arising at complicated stages of integration may produce new and unpredictable characteristics of the system.[6]

Opponents of reductionism comment that this approach leads to a gap between science and reality.[25] To date, the approach to most scientific research on rehabilitation after ACL reconstruction has been by reductionism, analyzing separate training parameters. An integrated scientific approach that better reflects the complex biological effects of exercise training is lacking.[25]

This first part of the general discussion will present a scientific evaluation of the standardized accelerated brace-free rehabilitation after ACL reconstruction used in the clinical studies of this thesis (Appendix 1). If necessary, recommendations for improvement of this rehabilitation protocol will be made for specific rehabilitation components.

Preoperative rehabilitation & timing of ACL reconstruction

Targeted preoperative therapeutic exercise programmes have been shown to reduce surgical complications, shorten hospital stay and accelerate the recovery of physical functioning after various types of elective surgery.[78, 123, 164] This concept is referred to as 'better in-better out' and requires an active involvement of both the patient and all related healthcare professionals.

The accelerated brace-free ACL rehabilitation protocol by Shelbourne&Nitz starts at the time of injury and preoperatively includes aggressive swelling reduction, hyperextension exercises, gait training and mental preparation.[149, 152] The least risk of knee arthrofibrosis after surgery occurs if the patient has minimal knee swelling, regained full ROM and normal gait before ACL reconstruction is performed.[44, 80, 109]

Other authors have confirmed the value of this so-called prehabilitation before ACL reconstruction.[39, 42, 52, 59, 148]
Shaarani et al. have shown that a 6-week progressive prehabilitation before ACL surgery led to improved knee function based on the single-leg hop test and self-reported modified Cincinnati score at 12 weeks after ACL reconstruction.[148]

Grindem et al.[59] compared preoperative and 2-year postoperative patient-reported knee function in patients who underwent progressive preoperative and postoperative rehabilitation versus usual care. The progressive preoperative protocol recommended regaining 90% quadriceps and hamstring strength, as well as hopping performance prior to ACL reconstruction. This patient group had superior preoperative patient-reported knee function, and still exhibited superior scores 2 years after surgery, with 86-94% of patients scoring within the normative range in the different subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS).[59]

Eitzen et al. concluded that patellar tendon autograft ACL reconstruction should not be performed before quadriceps muscle strength deficits of the injured limb were less than 20% of the uninjured limb.[39]
Gokeler et al. have confirmed this findings.[52]

These recommendations have been included in the Evidence Statement Rehabilitation after ACL Reconstruction of the Royal Dutch Society for Physical Therapy (KNGF).[42] This statement by Engelen-van Melick et al.[42] is the current national guideline for rehabilitation after ACL reconstruction in the Netherlands.

The goals of preoperative rehabilitation as defined in the standardized accelerated brace-free rehabilitation protocol of this thesis cohere with current scientific insights into ACL rehabilitation.

Brace & weight-bearing

The rationale of a postoperative knee brace is to protect the healing graft during the early phases of rehabilitation.[7] Various systematic reviews could not substantiate this hypothesis based on clinical results.[7, 96, 118, 165, 172] In vivo strain measurements of the native ACL have shown that a brace was not able to reduce the strain produced during application of an internal torque about the tibia in weight-bearing conditions.[95]

Functional knee bracing may even have negative consequences. In a 3D lower extremity-kinematic and electromyography study of treadmill running with or without functional knee brace use, the braced knees showed a decreased ROM, increased hamstring activation and decreased quadriceps activation.[118]

The systematic review in chapter 2 has shown evidence that early aggressive brace-free rehabilitation after hamstring tendon ACL reconstruction did not alter clinical outcome compared to nonaggressive rehabilitation.[28, 87] Knee-bracing following ACL reconstruction is neither necessary nor beneficial and adds to the costs of the procedure.[96] Furthermore, full weight-bearing without crutches within 10 days (after attaining a normal gait pattern) improves quadriceps function, prevents patellofemoral pain and does not affect knee stability.[103, 165, 172] Normal gait minimizes changes in knee biomechanics and may potentially influence the development of osteoarthritis.[51]

The goals of weight-bearing as defined in the standardized accelerated brace-free rehabilitation protocol of this thesis are in accordance with current scientific ACL rehabilitation insights.

Range of motion (ROM)

Long-term studies of an accelerated rehabilitation protocol after patellar tendon autograft ACL reconstruction have demonstrated that full ROM, equal to that of the opposite normal knee, is the decisive factor of long-term patient satisfaction.[4, 151, 152] In order of importance, the lack of normal knee ROM (within 3° of extension and 5° of flexion compared to the contralateral knee), partial or total medial meniscectomy, partial or total lateral meniscectomy, and articular cartilage damage are related to lower subjective scores. Patients with deficient extension and flexion reported the worst subjective scores.[151]
Regardless of the graft source, rehabilitation after ACL reconstruction must first strive to achieve full symmetrical knee ROM before aggressive strengthening is started.[152]

Regaining full knee extension to 0° after ACL reconstruction is important in the accelerated brace-free rehabilitation protocol of this thesis. However, hyperextension was regarded as harmful for the reconstructed graft. This caution may have been related to the nonanatomic ACL reconstructions of the 1990's. The transtibial surgical technique did not allow for consistent anatomic femoral tunnel placement and a notchplasty was recommended to prevent graft impingement in full knee extension.[73-77]

The long-term study presented in chapter 7 has shown that the number of patients with symmetrical ROM defined as IKDC Grade A (International Knee Documentation Committee; ROM difference < 3° extension and < 5° flexion compared to the contralateral knee) decreased from 94.2% preoperatively to 90.7% postoperatively.[86] Although pre- and postoperative ROM was not significantly correlated with long-term osteoarthritis after hamstring tendon ACL reconstruction, the correlation between ROM and patient satisfaction was not investigated.[86]

The problem of ACL graft impingement that was related to nonanatomical ACL reconstruction in the past has been largely resolved by the current techniques in anatomic ACL reconstruction. Anatomic ACL reconstruction facilitates impingement-free graft placement with less concern for graft abrasion in knee hyperextension.

Recommendation: The importance of symmetrical knee ROM for long-term patient satisfaction (regardless of the graft source) suggests that normal ROM (within 3° of extension and 5° of flexion compared to the contralateral knee) should be the goal after ACL reconstruction.

Strengthening exercises

Regaining full ROM and minimizing swelling of the knee are prerequisites before aggressive strengthening is started.[52, 152] The rationale of a strengthening training programme is to ensure that the injured leg reaches an acceptable muscle strength in order to minimise overuse and/or acute injury when returning to sports or strenuous work.[157]

Muscle strength and hop performance are commonly reported as limb symmetry index (LSI).[157] It has been demonstrated that patients with a quadriceps LSI < 85% had a decreased function, while those with LSI ≥ 90% showed functional performance similar to uninjured individuals.[52, 143]
Thomée et al. recommended a quadriceps and hamstring LSI of 100% as well as a 90% LSI hop performance prior to return to contact sports after ACL reconstruction.[157]

Closed kinetic chain (CKC) or weight-bearing exercises can provide superior integrated lower extremity neuromuscular recruitment and ease of composite strength or power measurement.[118] CKC exercises produce co-contraction of the muscles surrounding the joint and compression within the joint and therefore cause more joint stability.[154] Examples of CKC quadriceps exercises are double- and single-leg squats, squat lunges and leg-press exercises. In the postoperative phase of ACL reconstruction, pain, disuse and altered afferent input from mechanoreceptors in the operated joint reduce the efferent input to quadriceps thereby diminishing quadriceps activation.[64] Initially, patients tend to unload their affected knee after ACL reconstruction when performing squat exercises.[169] This tendency to unload has been associated with decreased bone mineral density in all areas of the knee in the first year after ACL reconstruction.[166] More symmetrical CKC loading patterns were achieved by inducing bilateral fatigue.[169]

Open kinetic chain (OKC) or non weight-bearing exercises can provide superior isolated muscle or muscle group recruitment and ease of strength measurement.[154] An example of an OKC quadriceps exercise is leg extension. The prescriptive use of CKC and OKC exercises enables patients to develop the dynamic lower extremity stability and neuromuscular control needed to protect the healing graft.[118] Biomechanical reviews of native ACL strain and tensile forces found similar maximum ACL strain values produced by squatting (CKC) and active flexion-extension (OKC).[22] Increasing resistance during squat exercises did not produce a significant increase in native ACL strain values, unlike increased resistance during active flexion-extension exercises.[22] OKC exercises generally loaded the ACL more than CKC exercises and that, for both exercises, the ACL was loaded to a greater extent between 10° and 50° compared to 50° and 100° of knee flexion.[43]

There has been concern that quadriceps strengthening might result in stretching of the ACL graft after accelerated rehabilitation.[87]
Beynnon et al.[23] demonstrated that there were no significant differences in subjective and clinical outcome after accelerated versus nonaccelerated rehabilitation after patellar tendon autograft ACL reconstruction, evaluating knee joint laxity using roentgen stereophotogrammetric analysis. The authors noted that still needs to be defined how quickly the frequency and magnitude of quadriceps activity can be increased after ACL reconstruction without the risk of increased anterior knee laxity.[23]

Kruse et al. published a systematic review on timing and safety of strengthening exercises after hamstring tendon and patellar tendon ACL reconstructions.[96] The authors concluded that accelerated brace-free rehabilitation did not show any deleterious effects compared with standard rehabilitation. It was likely to be safe for patients to begin immediate postoperative CKC exercises in a ROM 0°-90° and perform CKC quadriceps strengthening exercises. Eccentric quadriceps muscle strengthening and isokinetic hamstring muscle strengthening were safely incorporated 3 weeks after surgery.[96]

This thesis demonstrated that progressive concentric and eccentric exercises from 12 weeks postsurgery did not alter the clinical outcome after hamstring tendon ACL reconstruction.[87, 92] Various reviews have shown that eccentric strengthening exercises were most effective in restoring quadriceps strength, however it may not fully recover, even after 1 year.[52, 70, 98] Therapeutic exercises that emphasize eccentric gluteus maximus, quadriceps and gastrocnemius-soleus activation can improve lower extremity muscular shock absorption, prevent knee reinjury, enhance athletic performance, help heal lower extremity musculotendinous injuries, increase bone mineral density and decrease fall risk.[118]

This thesis has shown that early weight-bearing and the incorporation of CKC and OKC exercises at the appropriate time frames continue to have growing support.[4, 154]
Van Grinsven et al. concluded in their systematic review on evidence-based rehabilitation after ACL reconstruction that there is increasing consensus that OKC exercises have a favorable effect on quadriceps strength and do not increase graft laxity.[165]

Heijne et al.[67] examined the influence of early (4 weeks) and late start (12 weeks) of OKC quadriceps exercises after both hamstring tendon and patellar tendon ACL reconstruction. The early group started with OKC quadriceps exercises from 40°-90°, increasing ROM to 0°-90° after 5 weeks with unlimited external resistance according to symptoms and patient tolerance. The late group started OKC quadriceps exercises from 0°-90° at 12 weeks. External resistance was added from week 13. In contrast to the findings by van Grinsven et al.[165], early start of OKC quadriceps strengthening after hamstring tendon autograft ACL reconstruction resulted in significantly increased anterior knee laxity in comparison with both late start, and with early- and late start after patellar tendon autograft. This higher mean difference of laxity over time was 1.2 mm (CI:0.37-2.1). Furthermore, the early introduction of OKC quadriceps exercises did not influence quadriceps muscle torques in either group. The authors could not define the appropriate time to start OKC quadriceps exercises for patients after hamstring tendon ACL reconstruction and concluded that the choice of the graft affected the strength of the specific muscle more than the type of exercises performed.[67]

This influence of graft choice on isokinetic muscle strength after ACL reconstruction is in agreement with the systematic review by Xergia et al.[173] A meta-analysis of 14 studies demonstrated that patients with patellar tendon graft showed a greater deficit in quadriceps muscle strength and lower deficit in hamstring muscle strength compared to patients with hamstring tendon ACL reconstructions. The deficits were associated with the location of the donor site and still unresolved at 2-year follow-up.[173] Hamstring tendon autografts seem beneficial for quadriceps strength after ACL reconstruction.[52, 64]

A serious limitation of the aforementioned studies is that anterior graft laxity difference was the primary outcome for knee instability.
The consequences of various CKC versus OKC exercise programmes on functional (rotatory) instability after ACL reconstruction might be much more relevant for clinical purposes. Experimental efforts to quantify rotatory instability of the knee after ACL reconstruction are noteworthy, but clinical applications are very limited to date.[26, 60, 146] Further research is necessary to determine the optimal timing of introducing OKC quadriceps exercises and safe amount of specific resistance training after hamstring tendon ACL reconstruction.[7, 165]

Accelerated rehabilitation & osteoarthritis
Knee osteoarthritis (OA) is a long-term concern after ACL reconstruction.[86] Majima et al.[103] performed a prospective comparative study between accelerated and conservative rehabilitation after hamstring tendon ACL reconstruction. In agreement with the aforementioned studies on quadriceps strengthening, they demonstrated that accelerated rehabilitation restored muscle strength more rapidly than did conservative rehabilitation without compromising graft stability. The authors argued that early restoration of muscle strength might be beneficial for professional or competitive athletes. However, the incidence of synovitis of the knee was significantly increased after accelerated rehabilitation.[103] By 9 months, there was no longer any significant difference in muscle strength between the two types of rehabilitation. The authors comment that the higher incidence of problematic joint effusions, and consequently the increased levels of degradative enzymes, may negatively affect cartilage and ACL graft tissue in the accelerated rehabilitation group.[103]

Excessive knee loading has been implicated in the development and progression of OA.[144] Postoperative rehabilitation after ACL reconstruction should not be accelerated without limits because synovitis of the knee is frequently induced.[117] Increased synovitis after accelerated rehabilitation, and consequently increased levels of degradative enzymes that may cause cartilage decay, is associated with long-term OA.[103]

Synovitis of the knee should guide the pace of rehabilitation. Since an initial delay in restoration of muscle strength does not seem to be a lasting disadvantage, a more conservative strengthening rehabilitation protocol after hamstring tendon ACL reconstruction may be warranted also considering the findings of this thesis that human hamstring ACL graft remodelling is delayed compared with animal studies on which current rehabilitation protocols are based.[82, 87, 88, 103] Furthermore, quadriceps muscle weakness is not a risk factor for long-term OA.[121]

This thesis has shown that 53.5% of patients developed radiological OA of the knee at 10-year follow-up after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation.[86] Synovitis was not studied as risk factor for osteoarthritis in this study. Cartilage condition and previous meniscectomy were important determinants for OA. The rate of OA after meniscectomy and ACL reconstruction was 64.5% in comparison to 20% in the group with isolated ACL reconstruction. Predictors for OA were patient age ≥ 30 years at time of ACL reconstruction, cartilage status ≥ ICRS (International Cartilage Research Society) grade 2 at time of ACL reconstruction, history of medial meniscectomy and preoperative one-leg hop test C and D. Multivariate logistic regression analysis showed the status of the medial meniscus and ICRS grade 3 cartilage condition at time of ACL reconstruction to be significant predictors for knee OA.[86]

Knee OA is a multifactorial process. Graft choice has also been correlated to knee OA in the long-term after ACL reconstruction.[129, 130] This thesis has shown that patellar tendon autograft is associated with an increased risk of developing early signs of OA.[87] Other reviews have focused on OA after ACL reconstruction and found similar findings.[163, 174]

Controversy exists in the correlation between risk of knee OA and female sex. Some authors described an increased risk of developing OA in women.[122, 176] More recent studies suggested equal risk of OA in both men and women[18] as well as an increased risk in males following ACL injury.[99] However, women demonstrated more knee laxity compared to men with greater biomechanical asymmetries.[36, 79] Female sex predisposes to ACL injury, however, it remains unclear whether female sex predisposes to poorer outcome after ACL reconstruction.[137]

The ACL reconstruction technique used in this thesis is nowadays recognised as a nonanatomic reconstruction.[86] The influence of anatomy of reconstruction in the present study could not be analysed due to the lack of long-term evidence of prevention of OA after anatomic ACL reconstruction. Considering the multifactorial etiology of OA, these findings should be cautiously interpreted. Studies on long-term knee OA after ACL reconstruction have shown various results.[86] Øiestad et al. concluded in a review that differences in study design, radiological definition and classifications of OA may lead to a wide range of OA rates.[86, 120] More high-quality RCT studies with strictly specified inclusion criteria are needed to determine long-term OA after ACL reconstruction with accelerated brace-free rehabilitation.[174]

Recommendation: CKC quadriceps exercises are preferred in the first 12 weeks of rehabilitation after hamstring tendon ACL reconstruction. Start CKC exercises in 50°-90°, gradually building ROM to 0°-90° and resistance as tolerated. Inducing bilateral fatigue improves loading symmetry in CKC exercises. A combination of CKC and OKC quadriceps exercises is recommended. It is safest to start OKC quadriceps exercises at 12 weeks in 0°-90°, adding progressive concentric and eccentric exercises at 13 weeks. Eccentric training is recommended for quadriceps strengthening exercises. Focus of training should be on both legs. Synovitis of the knee should guide the rehabilitation pace.

Neuromuscular training

This thesis showed that neuromuscular characteristics of the operated leg were markedly different from the noninjured leg after hamstring tendon ACL reconstruction.[87] There is significant evidence indicating that altered biomechanics are present after ACL reconstruction during ADL (walking, going up and down stairs) and are even more pronounced in athletic activities, such as jumping.[53-56] Engelen-van Melick et al.[41] have shown that the occurrence of dynamic knee valgus in landing from a jump is higher in operated subjects compared with healthy controls up to 9 years after ACL reconstruction, irrespective of graft type. These neuromuscular and biomechanical changes could increase the risk for a second injury to both the operated as well as the contralateral knee.[54, 87, 125, 127] Engelen-van Melick et al. emphasized the need for focus on quality of movement as part of ACL rehabilitation and return to sports criteria.[41]

Neuromuscular training helps to develop finely tuned motor programmes and activation sequences that occur before and during stressful knee joint loading.[118] There is an increased recognition that dynamic knee joint stability needs to be improved through enhanced neuromuscular control mechanisms to prevent athletic knee injury or reinjury.[53, 54, 118]

Kruse et al.[96] concluded in their systematic review that neuromuscular interventions were unlikely to be harmful. The authors also concluded that neuromuscular training was unlikely to help patients to return to sports faster.[96] Neuromuscular training should not be performed to the exclusion of strengthening and knee ROM exercises.[4, 96] Neuromuscular training should be added to a strengthening training programme to optimize patient-reported outcome measurements.[52, 136]

Gokeler et al.[54] described that a potential limitation of current rehabilitation protocols after ACL reconstruction could be a deficiency in the transition from conscious awareness achieved during rehabilitation sessions to unexpected and automatic movements required for athletic activities on the field. Learning strategies with an internally directed focus have traditionally been used but may be less suitable for acquisition of control of complex motor skills required for return to unrestricted sports.[53, 54] The authors suggest that an externally focused neuromuscular rehabilitation strategy may enhance skill acquisition more efficiently and increase the potential to return to competitive sports.[54]

Recommendation: Most of the goals of neuromuscular training as defined in the standardized accelerated brace-free rehabilitation protocol of this thesis are in accordance with current scientific evidence on ACL rehabilitation. However, focus on quality of movement and externally focused learning strategies are important in ACL rehabilitation and should be emphasized.

Return to sports

After strengthening and neuromuscular goals are reached, patients can shift to sport-specific exercises and eventually return to sports.[24, 149, 152, 153]

Based upon anecdotal success, ACL rehabilitation protocols slowly evolved from a 12 months time frame for return to sports to a generally accepted 6 months time.[171] According to the accelerated rehabilitation by Shelbourne&Nitz, patients progressed from sport-specific activities to competition as they were comfortable.[149] It usually took 3 to 4 months of competition before the patient felt that they were competing at 100%. Even though the patients were back to their sports early, they had periods of knee stiffness and swelling that required periods of rest. The mean time when patients rated themselves as competing at 100% was 6.2 months after ACL reconstruction.[150]

In the standardized accelerated brace-free rehabilitation protocol of this thesis, a return to unrestricted sport activities was allowed at 4-6 months after ACL surgery. A recent study concluded that leading ACL experts generally let their patients return to play after an average of 6 months, with return to full competition after an average of 8 months.[106] In elite professional football, male UEFA-league players needed 7 months to return to the first training after ACL reconstruction, 10 months to return to regular practice and 12 months to return to match play.[132, 167]

Studies containing rehabilitation protocols with a duration of 6-10 months and training frequency of 2-3 times a week were more beneficial to improve quadriceps strength compared to programmes with a shorter duration and/or less frequency.[52] Feller et al.[47] noted that in assessing reported outcomes of ACL reconstruction, it should also be taken into account that clearance to return to sports at a certain time does not necessarily mean that patients actually returned

to sports at that time. The timing of the surgery with respect to the stage of the season may influence the return to participation. There may be an added incentive to return earlier in seasonal sports (e.g. at the start of the next season), compared to sports which are played all year round.[47]

Several factors must be evaluated when deciding to allow a patient to return to sports.[157] Creighton et al.[33] have outlined a decision-based return to play model comprising 3 steps.
Step 1 involves medical factors for evaluating the patient's health status, such as demographics, medical history, symptoms and signs. Step 2 involves sport risk modifiers (such as the type and level of sport) for evaluating risks if the patient returns to sports. Step 3 involves decision modifiers, such as season, internal and external pressure and conflict of interest.[33, 157]

Patient psychological factors are predictive of ACL reconstruction outcomes and return to sports.[12, 45] In a recent systematic review by Everhart et al.[45] self-confidence, optimism, and self-motivation were predictive of outcomes, which is consistent with the theory of self-efficacy. Stress, social support, and athletic self-identity were predictive of outcomes as well, which is consistent with the global relationship between stress, health, and the buffering hypothesis of social support.[45] Fear of reinjury or kinesophobia has been identified as significant factor in patients who did not return to their preinjury level compared to patients who did.[10, 12, 47, 66]

Ardern et al. found that patients with a delay of more than 3 months between injury and ACL reconstruction had a greater fear of reinjury compared to patients with surgery with a shorter interval from the time of injury.[10] Feller et al. speculated that this may be caused by the experience of recurrent episodes of giving way of the knee as time progresses.[47]

The rates of return to preinjury sports after ACL reconstruction are less than might be expected with an apparent rapid decline in sports participation after 2 to 3 years.[47]
The systematic review in chapter 2 has shown that after ACL reconstruction, the overall return to some kind of sports activity was 81%. Sixty-five per cent of patients returned to their preinjury level and 55% to competitive sports at final follow-up. Younger age, male gender and a positive psychological response all favoured returning to the preinjury level of sports. Elite athletes had more than twice the odds of returning to competitive sports compared to non-elite athletes.[11] Female gender, higher body mass index and smoking in the first 6 months prior to ACL reconstruction have been associated with lower return to sports.[38, 47]

Sandon et al.[139] found that female gender, cartilage injury and knee pain during physical activity were independent negative predictors for return to football after ACL reconstruction irrespective of graft type. For players with all three significant predictors, only 10% returned to football compared to 76.5% of the players without any of these predictive variables.[139]

Dunn et al.[38] found that a higher level of preinjury activity level was the strongest predictor of return to sports at 2-year follow-up after ACL reconstruction. This is in agreement with the findings by Zaffagnini et al.[177] These authors have shown a return to preinjury professional football level in 95% of elite male athletes after 1 year with accelerated brace-free rehabilitation.[177]

This thesis has demonstrated that few studies actually measured the ability to return to sports and its timing after ACL reconstruction.[96] Barber-Westin et al.[16] reviewed the factors used to determine return to unrestricted sports activities after ACL reconstruction. Only 13% of studies in their review described objective criteria required for return to sports. The authors concluded that there is a major lack of objective assessment before release to unrestricted sports activities in the literature.[16] Furthermore, commonly used muscle functional tests are not demanding or sensitive enough to identify differences between injured and noninjured sides.[17, 132]

In this thesis, only 35% of studies reported assessment criteria for return to sports after hamstring tendon ACL reconstruction.[87] These criteria however lacked specific details for use in clinical practice or comparative scientific research. Twenty-four percent of studies did not report when patients were allowed to return to sports without restrictions. Only 10% of studies reported whether patients were able to return at preinjury level.[65, 87]

Although scores may be high on validated clinical measures, the ability to return to sports and performance on return to sports may not meet up to the patient's expectations, thus making the surgery unsuccessful from the patient's perspective. This had been demonstrated in a meta-analysis of nearly 6000 patients after ACL reconstruction.[8] The study showed that only 44% of patients were able to return to competitive sport, despite 90% of patients having normal or nearly normal knee function using validated outcome scores.[9, 65] Ardern et al. suggested that greater emphasis should be placed on the use of participation-based outcomes to assess the effectiveness of ACL reconstruction rather than on impairment-based outcomes.[9, 52]

Return to sports & ACL graft rerupture rate
ACL reconstruction techniques have improved over the last 10 years, but graft failure is not uncommon: 0.7-10%.[81-83, 105] Clinical studies have shown that rerupture rates of ACL grafts are correlated with return to sports and occur in the first two years after reconstruction.[46, 110, 124-126, 155]
Faunø et al.[46] analysed 14,806 ACL reconstructed patients in the Danish Registry of Knee Ligament Reconstruction. Teenagers (13-20 years) showed a 3.5 times higher ACL revision rate compared to adult ACL reconstructed patients. A new trauma was the primary cause for ACL graft rupture.[46]

Paterno et al. analysed the incidence rate of ACL graft rerupture normalized to athlete-exposure in pivoting and cutting sports.[124-126] In these studies, the incidence rate provided a more accurate representation of ACL injury proportional to the amount of time that the athlete was at risk.[124]
A second-injury incidence density occurred in a young, active population at 1 year and 2 years after ACL reconstruction in relation to return to sports.[124-126] An athlete between the ages of 10 and 25 years who returned to a pivoting or cutting sport after ACL reconstruction, was 15 times more likely to sustain an ACL injury in the first 12 months than a previously uninjured athlete.[124, 125] Furthermore, the same population was 5 times more likely to suffer a second ACL injury in the first 24 months after return to sports compared with an uninjured cohort.[124, 126, 143]

Collectively, these data highlight the high risk of a second ACL injury in the early stages of return to sports after ACL reconstruction.[124] In fact, of the patients who suffered a second ACL injury, 30% experienced it in fewer than 20 athlete-exposures after return to sports, and more than 52% experienced it in fewer than 72 athlete-exposures.[124, 126]

This raises the question whether there is a misbalance between graft loading (level of sports activity) and graft healing. A delayed remodelling in human ACL grafts might be one of the reasons for this rerupture rate. While there is evidence that intra-articular remodelling of hamstring and patellar tendon autograft continues for up to 2 years after ACL reconstruction, data indicated that there is no significant improvement in function between 1-2 years.[71, 82, 88]

One could compare ACL graft healing with the principles of bone fracture healing. A specific amount of progressive loading is necessary at various stages after a bone fracture. Insufficient loading might lead to delayed union but excess loading might cause refracture of the bone. It is agreed that ACL graft healing can only progress if mechanical loading occurs: however, the most adequate magnitude at varying phases of healing is still not clarified.[81-83] The development of in vivo measurements of the mechanical properties of the healing ACL could enhance the research on time- and dose-specific loading of the ACL graft for optimal remodelling and safe return to sports.[29, 81-83]

Knowledge about the duration of the remodelling process of ACL grafts may further improve rehabilitation protocols. This thesis has shown that intra-articular hamstring graft remodelling takes at least 1 year after ACL reconstruction with an accelerated brace-free rehabilitation and was still active at 2 years.[82, 889, 83-85, 130] Animal and human ACL graft remodelling undergo the same three healing phases but human graft remodelling is prolonged compared to data from animal in vivo studies.[29, 81-83, 88, 128]

Since today's rehabilitation protocols have often been extrapolated from animal studies, current findings in human graft remodelling studies might require new postoperative regimens following hamstring tendon ACL reconstruction.[81-83] The current biological evidence on human graft healing does not support return to sports at 4-6 months after hamstring tendon autograft ACL reconstruction with accelerated brace-free rehabilitation.[82, 88] Recovery of activity level, function and subjective satisfaction all appear to plateau within the first 6 months of surgery.[71] Evidence of such a plateau offers opportunities for further research to define the optimal balance of graft loading and graft healing in the various rehabilitation phases after ACL reconstruction. This thesis has shown that despite the large number of peer-reviewed publications, no conclusive guidelines currently exist to determine when a safe return to unrestricted activity is permitted.[87]

A critical remark is necessary when accelerated rehabilitation after ACL reconstruction is discussed. The original accelerated brace-free rehabilitation program by Shelbourne&Nitz emphasized specific presurgical rehabilitation goals and a progressive postoperative scheme that allows patients to advance as they achieve quantifiable goals.[23, 24, 26, 46, 61-63, 151]

This thesis has shown that there is quite a variety in reported accelerated rehabilitation programmes after ACL reconstruction.[87, 178] Furthermore, few papers have described their protocol in detail.[73, 84, 87, 170] In accordance with the protocol by Shelbourne&Nitz[149], most studies on accelerated brace-free rehabilitation agreed that immediate weight-bearing, full ROM and CKC exercises were permitted after hamstring tendon ACL reconstruction.[87] However, if even specified at all, the protocols varied in their timing and details of OKC exercises, frequency of concentric and eccentric training, neuromuscular training and timing of return to activities such as running or unrestricted sports often lacking specific criteria.[87]

The lack of details of accelerated rehabilitation protocols after hamstring tendon ACL reconstructions makes it difficult to evaluate the potential disadvantages of accelerated rehabilitation such as tunnel widening and increased synovitis.[103 30, 87, 162] Postoperative rehabilitation is a major factor contributing to the success of ACL reconstruction and needs to be defined in detail for adequate research on clinical outcome and safe return to sports. A shift needs to me made from the traditional time-based rehabilitation to a more customized protocol based on achieved quantifiable goals in phases of rehabilitation after ACL reconstruction.

The development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual return to sports is greatly needed and offers opportunities for further research.[11, 16, 40, 41, 69, 87, 118, 132, 157] Identifying specific patient phenotypes, possibly gender-related, may allow a more customized rehabilitation approach. Studies identifying sport-specific differences in ACL reconstruction outcomes in athletes could further enhance different time frames of rehabilitation after ACL reconstruction.[177]

Recommendation: The current biological evidence on graft healing does not support return to unrestricted sports at 4-6 months after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. Knowledge about the duration of the remodelling process of ACL grafts may further improve rehabilitation protocols. Future research will have to be directed to (1) optimizing ACL reconstructions to fully restore the anatomy and function while providing the mechanical strength of the intact ACL, (2) developing biological treatment options that impact on graft healing especially during the early and proliferation phase to optimize extracellular matrix remodelling and avoid excessive remodelling activity that might impair mechanical integrity of the healing graft and (3) to better differentiate the 'good' from the 'bad' remodelling changes, so that the time to return to sports without any restrictions can be reduced.[81-83]

ACL graft remodelling and tendinopathy: new horizons

Tendon graft healing is an important determinant for rehabilitation and return to sports after ACL reconstruction. This thesis has shown novel insights in the remodelling of hamstring tendon ACL autografts but there is still a lack of knowledge on the biology of graft healing. Human in vivo biopsy studies are limited and ethically difficult to perform.[81, 83, 88] A better understanding of the properties and remodelling of ACL tendon grafts is necessary to optimize the outcome after ACL reconstruction.

At the recent 25th Anniversary NVA Congress (Nederlandse Vereniging voor Arthroscopie - Dutch Arthroscopy Society), I was fascinated by new research developments on tendinopathy. Speakers at this meeting were G.P. Riley PhD., J. Zwerver MD, PhD and P.W. Ackermann MD, PhD. The striking similarities between tendinopathy models and ACL hamstring tendon graft remodelling inspired me to contemplate new horizons in ACL remodelling and rehabilitation research. To my knowledge, this association has not been made before.

In the next part of the discussion, an overview of current knowledge on tendinopathy will be presented with illustration of the similarities between tendinopathy and ACL hamstring tendon graft remodelling. Fields of interest for future research will be highlighted.

Tendon structure and function

Tendons are metabolically active tissues and are 'engineered' according to the functional demands on them in specific anatomic locations.[1] The organization of tendons follows a strict hierarchical pattern.[102] Collagen molecules are organised precisely to give rise to the characteristic 67 nm D-periodization that forms fibrils. The collagen molecule is ~300 nm in length and 1.5 nm in diameter, and aggregated molecules of the fibril are stabilized by covalent intermolecular crosslinks.[15, 19, 90] The crosslinks bind the collagen molecules to one another and thereby confer integrity on the fibril. The collagen fibril is considered the fundamental force-transmitting unit of the tendon, although the actual length of fibrils in mature tendon remains an unresolved issue.[102] Groups of fibrils then form fibres known as fascicle bundles, which finally comprise the tendon proper.[102]

The collagen fibril is embedded in a hydrophilic extracellular matrix.[102] This extracellular matrix consists of: (1) collagen (65 to 80% dry weight), which is mostly composed of type I collagen and provides the tendons with strength to withstand high loads[134]; (2) elastin (1 to 2%), which insures flexibility and elastic properties; and (3) ground substance, which consists of approximately 60 to 80% water, proteoglycans and glycoproteins.[1]

The cellular component is represented by tenoblasts and tenocytes, which are arranged in parallel rows between the collagen fibers. Tenoblasts are immature spindle-shaped tendon cells, containing abundant cytoplasmic organelles, reflecting their high metabolic activity. This thesis has shown that these spindle-shaped tendon cells have also been found in the hamstring tendon grafts between 1-2 years after ACL reconstruction, suggesting that remodelling of ACL grafts was still active after 1 year.[82, 88]

As they age, tenoblasts become elongated and transform into tenocytes. Together, tenoblasts and tenocytes account for 90 to 95% of the cellular elements of tendons. The remaining cellular elements consist of chondrocytes, synovial cells and endothelial cells.[1]

Appropriate compliance is required by the energy-storing tendons to allow stretching and recoil to occur in pace with the gait cycle. These energy-storing tendons have a higher noncollagenous protein content, predominantly proteoglycan, which is thought to allow sliding movement between collagen fibrils.[158] Maintenance and regeneration of the physiological biochemical composition of the collagenous and noncollagenous extracellular matrix are essential for optimal structure and function of the tendon.[35]

The interfascicular space contains fibroblasts (tenocytes), capillaries, nerves and small-diameter fibrils. It remains unknown if the structures in this space would be adversely affected by disproportional large shear or focal adhesions, or both.[102] During tensile loading, fibroblasts and their cell nuclei, located between fibrils and the interfascicular space, undergo deformation, which might play an important role in the mechanical signal transduction pathway of the tendon.[14, 145] Loading can potentially place strain on several components of the tendon that might contribute to an injury that requires repair. Such a repair process might compromise a fine balance between synthesis and degradation of the various components of the extracellular matrix.[102] However, it should also be noted that too little stimulation (relative inactivity) might also affect such an anabolic-catabolic balance.[13] This balance of 'response to loading' has also been shown to be important during the remodelling of the extracellular matrix of ACL hamstring tendon grafts in this thesis.[82]

Human tendons typically have a fracture stress of ~100 MPa. However, most tendons are only subjected to stresses of up to ~30 MPa, which gives tendons a reasonable safety margin.[102] Tendon microrupture, which is presumably associated with a lack of load in a local area along with its associated fibroblasts, has been suggested as a possible injury mechanism for tendinopathy.[115] The average tensile stress (which relates to the force transmitted and the area over which it is transmitted) exerted on a tendon will depend on its cross-sectional area[102] and length.[1] The greater the cross- sectional area of a tendon, the larger its capacity to withstand heavy loads before failure.[1, 102] This is in agreement with studies on rerupture rates of ACL tendon grafts as presented in this thesis. A larger cross-sectional area of the ACL graft is associated with lower rerupture rates.[85] With increasing tendon fibre length, the stiffness decreases and the force to failure remains the same, but elongation to failure increases.[1]

If one neglects viscoelastic properties, a typical stress-strain curve of tendons can be drawn.[1, 93] At rest, the collagen fibres and fibrils of the tendon are in a wavy or crimped configuration. Crimp provides a buffer in which slight longitudinal elongation can occur without fibrous damage, and acts as a shock absorber along the length of the tissue.[100, 133] As the collagen fibres deform, they respond linearly to increasing tendon loads.

At up to approximately 4% elongation, the fibres regain their original configuration after the tension is released. If the tendon is stressed beyond 4% of its length, the collagen fibres start to slide past one another as the intermolecular crosslinks fail, and, at approximately 8% of elongation, a macroscopic rupture occurs because of tensile failure of the fibres and interfibrillar shear failure.[1]

In vivo strain measurements of native ACLs in commonly prescribed rehabilitation exercises have been analysed in healthy volunteers.[95] ACL peak strain values varied from 0% to 4.4% for CKC and OKC exercises. Only isometric quadriceps contraction at 15° of knee flexion exceeded the peak strain value of 4% at which tendon collagen fibres start to slide past one another as the intermolecular crosslinks fail.[1] All other rehabilitation exercises were within the safe zone for tendon elongation.[95]

Future research is necessary to define peak strain values of rehabilitation exercises in ACL reconstructed knees to define the optimal 'response to loading' for tendon graft remodelling after ACL reconstruction.

Tendon response to load

Tendons are metabolically active and respond to both loading and unloading. The collagen protein synthesis response is regulated by strain on tenocytes, independent of the muscle contraction mode (eccentric, isometric or concentric).[68] Mechanical loading results both in collagen protein synthesis and degradation of collagen.[102]

Mechanical loading of tendon tissue is anabolic by upregulating collagen gene expression and increasing synthesis of collagen proteins. This peaks around 24 hours after exercise and remains elevated for up to 70–80 hours.[2, 102] However, exercise also results in degradation of collagen proteins and this catabolic peak occurs earlier and to a greater extend than the anabolic peak.[2, 102] The result is a net loss of collagen around the first 24–36 hours after training, followed by a net gain in collagen.[102] This data indicates that a net increase in collagen requires a certain restitution period, and that without sufficient rest, a continuous loss of collagen may occur. Insufficient rest (at least 24 hours) after exercise will cause net loss of collagen and may cause tendon vulnerability to injury.[102]

Studies on tendinopathy have shown that tendon response in type I collagen precursors peaks around 3 days after a single bout of intensive exercise suggesting that time interval for adaptive response is an important factor.[32] Tendon load without energy storage and release, such as cycling or strength-based weight training, can be maintained, as this is less likely to induce further tendon response. Conversely, high-load elastic or eccentric loading, particularly with little recovery time (e.g. on successive days), will tend to aggravate tendinopathy in this stage.[32] Furthermore, there is a ceiling effect in collagen synthesis indicating that fibroblasts are unable to further synthesize collagen beyond an upper limit. Adding exercise repetitions beyond this limit potentially increases degradation, amplifying a catabolic state in tendon collagen content and tendon vulnerability.[102]

A tendon is able to adapt to load linked with the specific function of anatomic structures in and around the tendon (tendon cells, tenocytes, extracellular matrix and nerve-ending receptors).[2, 3] Habitual training results in a higher turnover of collagen, whereas inactivity lowers collagen synthesis and turnover. In addition to collagen, other matrix proteins such as proteoglycans respond to loading. The expression of enzymes involved in protein crosslinking is also upregulated with exercise. As such, loading activity maintains tendon homeostasis and supports the use of loading activity in the treatment of tendinopathy.[102]

In view of this tendon adaptation to load as well as the ceiling effect in collagen synthesis by fibroblasts, it would be interesting to study the development of preoperative strategies to increase the collagen content in hamstring tendons prior to their use as ACL tendon grafts. This could increase ACL tendon graft strength and might decrease the rerupture rates of ACL grafts in sports-related activities.

Cook et al.[32] developed a pathology model to explain the clinical presentation of load-induced tendinopathy. This model shows tendon pathology to be a continuum although 3 distinct phases have been described with continuity between the 3 phases.[32] Adding or removing load is the primary stimulus that drives the tendon forward or back along the continuum, especially in the early stages. Within the constraint of recovery proposed in this model, reducing load may allow the tendon to return to a previous level of structure and capacity within the continuum.[32] These phases in tendinopathy show similarities with the 3 phases of ACL hamstring tendon graft remodelling as described in this thesis.[82]

Müller et al.[114] described that healed tendon tissue rarely achieved functionality equal to that of the preinjury state. The final tensile strength of healed tendons may be reduced by up to 30%.[114] After ACL reconstruction, not a single animal study has demonstrated that the structural properties (e.g. failure load, stiffness) of the healing graft could surpass 50–60 % of the intact ACL.[82] No such data is available from human in vivo studies. It might be expected that final ACL graft strength is not better in humans considering the fact that ACL hamstring tendon remodelling in humans was prolonged compared to animal studies in this thesis.[82, 88]

Pain is a symptom for load-induced tendinopathy. After ACL reconstruction, pain and swelling are comparable symptoms for a necessary delay in rehabilitation. Since self-confidence was predictive for outcome after ACL reconstruction, one might question if the patient's self-efficacy could also be a monitor system to guide rehabilitation and graft healing.[45]

The application of existing research models on tendinopathy to ACL graft remodelling could enhance knowledge on graft healing response to rehabilitation loading in various stages after ACL reconstruction. This offers new horizons in ACL tendon graft remodelling research since in vivo biopsy studies are ethically difficult to perform in humans.

On a molecular level, exercise leads to increase in mRNA levels and tissue concentrations of growth factors in the tendon and the peritendinous tissue that stimulate collagen synthesis (e.g. transforming growth factor (TGF-β), insuline-like growth factor (IGF)-1, connective tissue growth factor (CTGF) interleukin (IL)-6).[2, 102]

Estrogen is shown to be an inhibitor of IGF-1 and this might be a reason why women show less increase in collagen synthesis, need longer for tendon adaptation to loading and are more susceptible to soft tissue (re) injuries than men.[62, 63, 102, 107, 108] As collagen content is related to strength of the ACL tendon graft, this estrogen-related collagen synthesis may necessitate different rehabilitation strategies for men and women for optimal ACL graft healing. Future gender-based research might lead to better outcome after ACL reconstruction.

IGF-1 is a key regulator for collagen synthesis in both loading and unloading of the tendon. Inactivity by lower limb casting in humans resulted in an initial increase in the levels of IGF-1 mRNA, indicating an unloading response. The expression of collagen is again normalised after resumption of activity.[138] Magnusson et al.[102] postulated that this might be explained as a compensatory increase in the synthesis of growth factors to counteract the inactivity-induced decrease in collagen synthesis. Inactivity does not follow a pattern opposite to that of a loading response, and this pattern might reflect a protective mechanism towards the loss of tendon tissue during inactivity. They concluded that these responses do not favor inactivity as treatment for tendinopathy.[102]

This is comparable to the knowledge on hamstring tendon graft healing after ACL reconstruction in this thesis. It is agreed that ACL graft healing can only progress if mechanical loading occurs: however, the most adequate magnitude at varying phases of healing is still not clarified.[81–83] Accelerated brace-free rehabilitation needs to be as aggressive as possible in restoring function while still maintaining an optimal tissue healing environment.[118]

The development of in vivo measurements of the mechanical properties of the healing ACL tendon graft could enhance the research on time- and dose-specific loading of the ACL graft for optimal remodelling and safe return to sports.[29, 81–83] Could imaging techniques in tendinopathy be helpful for this purpose?
Imaging in tendinopathy has mostly been performed in studies on Achilles- and patellar tendinopathy with magnetic resonance imaging (MRI) and ultrasound. The studies have shown characteristic pathological changes in tendinopathy with tendon thickening or swelling, with localized hypo-

echogenic signals on ultrasound and increased T1 and T2 contrast signals on MRI.[94, 104, 111, 112, 156] These signals are associated with higher water content which is possibly related to increased accumulation of water-retaining proteoglycans.[49] Doppler ultrasound imaging showed increased vascularity and blood flow in pathological regions but the oxygen tension was not significantly different.[49, 156] These findings suggest an inflammatory component with localized changes in tendinous matrix and hypervascularity, associated with tendinopathy.[49]

Van Schie et al. have shown the value of Ultrasound Tissue Characterization (UTC) in tendinopathy imaging. The authors concluded that UTC is suitable for detection of: (1) in-situ tendon responses to load; (2) early diagnosis of injury or degeneration; (3) staging of histopathological stage of lesions; and (4) for objective evaluation of longitudinal effects of regenerative therapies.[141]

The role of UTC may be limited in ACL tendon graft imaging due to the limited depth of penetration. To date, UTC has not been applied in ACL graft healing imaging and this offers new horizons for research on in vivo measurements of ACL graft remodelling. New developments in tissue fluorescence, MRI-angiography and fluorescence arthroscopy may be of future value in ACL tendon healing research.[116, 158, 159] If proven valid, these imaging techniques may monitor treatment and biological effects in the remodelling phases of ACL grafts by time- and dose-specific loading of different rehabilitation modalities.

Pathogenesis of tendinopathy

Historically, the term tendinitis was used to describe chronic pain referring to a symptomatic tendon, thus implying inflammation as a central pathological process. However, traditional treatment modalities aimed at modulating inflammation have had limited success and histological studies of surgical specimens consistently show the presence of degenerative lesions, with either absent or minimal inflammation.[1] Inflammation and degenerative changes often coexist in the course of tendon disorders, and their relative contributions are difficult to dissect. Therefore, the definition of 'tendinitis' has been largely abandoned and the terms 'tendinosis' or, more generically, 'tendinopathy' are currently preferred.[1, 49, 101]

Clinically, most tendon problems present as ruptures or localised pain, often with stiffness and swelling.
Symptomatic tendinopathy refers to chronic localized pain with degenerative changes in the tendon as observed by imaging or histology; while asymptomatic tendinopathy is identified from rupture or partial rupture cases shown to be associated with nonsymptomatic preexisting degenerative changes.[49]

Midportion and insertional tendinopathy (enthesopathy) should be distinguished as two different clinical diagnoses.[2]

The pathogenesis of tendinopathy has been associated with extrinsic and intrinsic factors based on epidemiological studies and clinical observations. Extrinsic factors are overuse in sports, training errors, fatigue, environmental conditions and certain medications (fluoroquinolone antibiotics, statins, oral contraceptives, cyclosporines, and injected corticosteroids).[1, 2] Although sports activity is the most common source of tendinopathy, 1 of 3 patients with Achilles tendinopathy is not active in sports and upper extremity tendinopathy is mostly work-related.[3] Overuse as a risk factor for tendinopathy is not simply a quantitative increase in activities, but may also be attributed to improper gait or training errors.[49]

Among the intrinsic factors, several pathological conditions must be considered.[1] Tendinopathy has been associated with endocrino-metabolic disorders such as hormone replacement therapy, oral contraceptives and obesity.[1, 72] Hypertension was statistically associated only for women, whereas diabetes mellitus had a significant association with men younger than 44 years of age.[72] These findings suggest that factors influencing microvascularity may play a role in the development of tendinopathy[1, 2] and female gender and pregnancy have been associated with significant differences in tendon microcirculation in animal studies.[49]

In diabetes, advanced glycation end products (AGEs) accumulate in tendons due to condensation of glucose with amino groups.[58] Glycated tendons can withstand more load and tensile stress than nonglycated tendons, but the tissue becomes stiffer.[1, 5, 20] It has been shown that high amounts of AGEs cause a fusion of collagen fibrils which display larger diameters.[1] They also cause an upregulation of connective tissue growth factor in fibroblasts, which favors the formation of fibrosis over time in diabetic patients.[1, 27, 161]

Tendinopathy has also been associated with certain systemic diseases, neurological conditions, infectious diseases, chronic renal failure, hyperlipidemia, psoriasis, systemic lupus erythematosus, rheumatoid arthritis, hyperparathyroidism and hyperthyroidism.[1, 2, 48, 49] Aging decreases the mechanical properties of tendons, possibly due to reduced arterial blood flow, local hypoxia, free radical production, impaired metabolism and nutrition as well as accumulation of AGEs.[1] However, tendinopathy is not merely an age-related degeneration because similar pathological changes were observed in young people.[49]

Genetic predisposition seems related to the development of tendinopathy. The collagen type 5, alpha-1 (COL5A1) and tenacin-C genes encode the collagen alpha-1(V) chain and tenacin- C, which are important structural components in tendons and ligaments.[1, 2, 49] Variations in these genes, along with variations in the gene encoding matrix metalloproteinase-3 (MMP3), are related to chronic tendinopathy.[102] The collagen alpha-1(V) chain is involved in the assembly of collagen fibres, influences fibre diameter and variations may influence collagen strength.[102] Tenacin-C is involved in in the collagen response to mechanical loading in a dose-dependent manner.[102] Since these genes are also related to homeostasis of the tendon extracellular matrix, it has been suggested that genetic variants modify the susceptibility of tendons to matrix disturbance as seen in tendinopathy.[49] The precise role of these genes in the development of tendinopathy is still unclear.[2]

Interestingly, the genes encoding these proteins have also been associated with ACL ruptures.[31, 102, 147] This offers another opportunity for research to investigate if genetically-prone tendinopathy patients suffer more reruptures after autograft tendon ACL reconstruction. If so, these patients might benefit from allograft tissue instead of autograft tendons as ACL graft.

In summary, multiple factors play a role in the pathogenesis and healing of tendinopathy. Cook et al.[32] discussed in their continuum model that the variable response to tendon treatment in research studies might be explained to some extent through the existence of subpopulations of different pathologies in the investigated cohort. The individual factors as genetics, age, gender, cytokine and endocrino-metabolic activity, biomechanics and body composition may alter the progression forward or back in the continuum of tendinopathy. These factors have an important role in the response to treatment.[32] This concept may well be applicable to the remodelling of hamstring tendon grafts after ACL reconstruction. Future research in specific phenotype subpopulations, with well defined, standardized ACL reconstruction techniques and rehabilitation, may offer new horizons for optimal treatment and outcome after ACL reconstruction.

Histology of tendinopathy

Fibroblasts and tendon cells can transform into myofibroblasts if subjected to a combination of repetitive mechanical stress, proinflammatory cytokines and TGF-β.[2] Myofibroblasts are important cells for tendon healing and remodelling.[81-83, 88] Myofibroblasts have smooth muscle actin in their cytoplasm and are thus capable of creating forces required for tissue contraction. After the healing process is completed and the biomechanical stress is released on the myofibroblasts, these cells undergo programmed cell death (apoptosis). If this mechanism fails, myofibroblasts will propagate a hyperproliferative process, fibrosis, seen as prominent histological feature of tendinopathy.[2] These cells can induce and maintain a prolonged contracted state in peritendinous adhesions, which, in turn, may lead to constriction of vascular channels, with further impairment of circulation inside the tendon.[1, 50, 89, 119]

Hypoxia causes fibroblast hyperproliferation, leading to an upregulation of matrix metalloproteinases, which leads to degradation of the extracellular matrix.[2, 35, 131] In addition, hypoxia upregulates vascular endothelial growth factor (VEGF), leading to angiogenesis in the tendon, a major finding in tendinopathy.[2, 131]

Angiogenesis is speculated to be a causative factor for pain due to the accompanying ingrowth of sensory nerves from the parathenon with subsequent release of nociceptive substances (substance P, glutamate).[2, 3, 142] Upregulation of substance P and glutamate stimulate proliferation of fibroblasts and endothelial cells and convert fibroblasts into myofibroblasts. This further contributes to fibrosis, hypervascularization, hypercellularity and pain.[2] A disturbance in type I collagen protein synthesis occurs leading to decreased type I and increased type III collagen content, further decreasing the material properties of the tendon.[57, 102, 133, 135] Interestingly, increased collagen III synthesis has also been associated with impaired mechanical strength of ACL grafts even after 2 years of healing.[34, 42, 45, 52] In addition, myofibroblast activity also occurs in ACL tendon graft remodelling. This thesis demonstrated continuous ACL hamstring tendon graft remodelling by myofibroblast activity up to 2 years after reconstruction. Similar to tendinopathy, collagen orientation did not return to normal in the study period after ACL reconstruction.[82, 88] The strength of the tendon is thus impaired.[81, 83] Myofibroblast activity is a good marker for active remodelling and future research should aim at detecting these cells as monitor for ACL tendon graft remodelling.[88]

In healthy nonpainful tendons, neuromediators are found in the paratenon, whereas the proper tendon is practically devoid of nerves, reflecting that normal tendon homeostasis is regulated by pro- and anti-inflammatory mediators from the tendon surroundings.[2, 3] During tendon repair however, there is extensive nerve ingrowth into the tendon proper and subsequent time-dependent appearance of sensory, autonomic and glutamatergic mediators, which amplify and fine-tune inflammation and tendon regeneration.[3] The process of nerve ingrowth in tendinopathy is unclear, but it seems to occur subsequently to disturbance in collagen protein synthesis, and might therefore explain why clinical pain occurs when the tendinopathy is already quite advanced.[102]

In tendinopathy, excessive and protracted sensory and glutamatergic signalling may be involved in inflammatory, painful and hypertrophic tissue reactions.[3] In tendinopathy, the ingrown nerves and blood vessels do not retract as in normal tendon healing.[102] This causes a larger cross-sectional area of pathological tendons compared to normal tendons as adaptations and load tolerance occurs in the surrounding aligned fibrillar structure.[37] Injection therapy in tendinopathy aims at reducing the pathological nerve ingrowth and neovascularization in the peritendinous area.[2] Treatment of the peritendinous area instead of the tendon proper has led to the concept of 'treat the donut, not the hole' by Docking et al.[37] Treatment strategies may be better served in building load capacity within the already present aligned surrounding tendon structure, rather than attempting to regenerate the area of pathology with intratendinous injections or surgery.[37]

Some authors propagate the importance of preserving remnant native ACL tissue at the footprints at time of ACL reconstruction for vascular en nerve ingrowth of the graft.[83] The idea is that accelerating angiogenesis of the healing ACL graft could promote faster graft healing.
However, in light of the findings in tendinopathy, where healthy tendons are aneuronal, and that neovascularization as well as nerve ingrowth are pathological factors in tendinopathy, one might question if this is to be recommended. Loss of collagen organization was only detected in areas of neovascularization in human biopsies, which corresponds to the findings in animal studies.[81-83, 88]

MRI studies have examined the revascularization of human hamstring autografts after ACL reconstruction.[13, 15, 19, 57] This thesis has shown that minimal debridement of the stump of the ruptured ACL led to earlier revascularization within the mid-substance of the ACL graft at 2 months, but found no evidence that the minimal debridement accelerated the recovery of graft strength.[82] In a gadolinium-enhanced MRI study, Howell et al.[19] did not demonstrate any discernible blood supply in an unimpinged 4-strand hamstring tendon ACL graft during the 2 years of implantation. The graft retained the same hypovascular appearance as the normal posterior cruciate ligament. In contrast, the periligamentous soft tissues were richly vascularized and covered the graft by 1 month.[19] This might reflect adequate ACL graft function considering the scientific evidence in tendinopathy research that healthy nonpainful tendons proper are devoid of nerves and neovascularization with normal tendon homeostasis regulated by pro- and anti-inflammatory mediators from the tendon surroundings.[2, 3]

This is also confirmed in a systematic review by Tohyama et al.[160] They examined the in vitro effects of VEGF treatment on hamstring ACL grafts in animals. VEGF treatment promoted a remarkable increase in synovial tissue with hypervascularity around the graft 12 weeks after ACL reconstruction and stimulated angiogenesis and cellular infiltration in the tendon. However, biomechanical properties of the graft deteriorated due to soft tissue flaws and digestion of graft matrix by the VEGF treatment. The authors recommended indirect enhancement of VEGF using physical stimulation as strategy to accelerate remodelling without weakening the ACL graft.[160]

This thesis has shown that biopsy studies of the peripheral structures of the hamstring tendon ACL autograft show typical phases of remodelling similar to the pathogenesis models of tendinopathy.[82, 88] As the centre of the graft seems to be less involved in healing and strength of the graft, prevention of neovascularization and pathological nerve ingrowth into the ACL tendon graft is a new area for research.

Future research on ACL tendon grafts must also focus on imaging, the mechanical properties and the time-dosed loading of peritendinous structures to monitor normal or pathological tendon healing after ACL reconstruction. This offers new horizons for optimal treatment and outcome after ACL reconstruction.

Clinical implications of this thesis

The aim of this thesis was to gain insights into the characteristics and biology of hamstring tendons as well as long-term clinical outcome after hamstring tendon autograft ACL reconstruction with accelerated brace-free rehabilitation.

The most important conclusion of this thesis is that current biological evidence on graft healing does not support return to unrestricted sports at 4-6 months after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. Graft healing is a prolonged process, which is still active after 1 year.

Accelerated brace-free rehabilitation starts preoperatively and should emphasize full ROM, gait training and quadriceps LSI < 20% before surgery. After surgery, a progressive scheme of function, strength and neuromuscular training allows patients to advance as they achieve quantifiable goals. The principles of immediate weight-bearing and early incorporation of CKC exercises apply, starting in ROM 50°-90°, gradually building ROM to 0°-90° with resistance as tolerated. Inducing bilateral fatigue improves loading symmetry in CKC exercises.

A combination of CKC and OKC quadriceps exercises is recommended. It is safest to start OKC quadriceps exercises at 12 weeks in 0°-90°, adding progressive concentric and eccentric exercises from week 13. Eccentric training is recommended for quadriceps strengthening exercises. Focus of training should be on both legs. Synovitis of the knee should guide the rehabilitation pace. Neuromuscular training and quality of movement are important in accelerated brace-free rehabilitation after ACL reconstruction.

Hamstring autograft length and size can be predicted in Caucasians based on anthropometric parameters. Hamstring tendons regenerate after harvest for ACL reconstruction. There was no relation between tendon regeneration and isokinetic flexion strength.
Long-term follow-up showed a significant improvement of clinical parameters and patient satisfaction after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. Hamstring tendon ACL reconstruction does not prevent long-term knee osteoarthritis: at 10-year follow-up, radiological signs of osteoarthritis were present in 53.5 % of the subjects. Risk factors for osteoarthritis were medial meniscectomy prior to or at the time of ACL reconstruction and cartilage injury (ICRS grade 3) at the time of ACL reconstruction.

The development of valid, criterion-based assessments to determine customized phases of rehabilitation and readiness for sport-specific training and return to sports is greatly needed and offers opportunities for further research. Identifying specific patient phenotypes, possibly gender-related, as well as identifying sport-specific differences in ACL reconstruction outcomes in athletes may further enhance a customized rehabilitation approach.

Scientific models for tendinopathy offer horizons for new research on ACL graft healing. Future research will have to be directed to (1) optimizing ACL reconstructions to fully restore the anatomy and function while providing the mechanical strength of the intact ACL, (2) developing biological treatment options that impact on graft healing especially during the early and proliferation phase to optimize extracellular matrix remodelling and avoid excessive remodelling activity that might impair mechanical integrity of the healing graft and (3) to better differentiate the 'good' from the 'bad' remodelling changes, so that the time to return to sports without any restrictions can be reduced.

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."
(Sir Winston Churchill, November 1942. Speech at London's Mansion House, just after the British routed Rommel's forces at Alamein, driving German troops out of Egypt)

References

1. Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V, Werner S, Paganelli R (2009) Pathogenesis of tendinopathies: inflammation or degeneration? Arthritis Res Ther 11(3):235

2. Ackermann PW, Renstrom P (2012) Tendinopathy in sport. Sports Health 4(3): 193–201

3. Ackermann PW, Franklin SL, Dean BJ, Carr AJ, Salo PT, Hart DA (2014) Neuronal pathways in tendon healing and tendinopathy-update. Front Biosci (Landmark Ed) 19:1251–1278

4. Adams D, Logerstedt DS, Hunter-Giordano A, Axe MJ, Snyder-Mackler L (2012) Current concepts for anterior cruciate ligament reconstruction: a criterion-based rehabilitation progression. J Orthop Sports Phys Ther 42(7):601–614

5. Akturk M, Ozdemir A, Maral I, Yetkin I, Arslan M (2007) Evaluation of Achilles tendon thickening in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 115(2):92–96

6. Andersen H (2001) The history of reductionism versus holistic approaches to scientific research. Endeavour 25(4):153–156

7. Andersson D, Samuelsson K, Karlsson J (2009) Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials. Arthroscopy 25(6):653–685

8. Ardern CL, Webster KE, Taylor NF, Feller JA (2011) Return to sport following anterior cruciate ligament reconstruction surgery: a systematic review and meta-analysis of the state of play. Br J Sports Med 45(7):596–606

9. Ardern CL, Taylor NF, Feller JA, Webster KE (2012) Return-to-sport outcomes at 2 to 7 years after anterior cruciate ligament reconstruction surgery. Am J Sports Med 40(1):41–48

10. Ardern CL, Taylor NF, Feller JA, Webster KE (2012) Fear of re-injury in people who have returned to sport following anterior cruciate ligament reconstruction surgery. J Sci Med Sport 15(6):488–495

11. Ardern CL, Taylor NF, Feller JA, Webster KE (2014) Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 48(21):1543–1552

12. Ardern CL, Osterberg A, Tagesson S, Gauffin H, Webster KE, Kvist J (2014) The impact of psychological readiness to return to sport and recreational activities after anterior cruciate ligament reconstruction. Br J Sports Med 48(22):1613–1619

13. Arnoczky SP, Lavagnino M, Egerbacher M (2007) The mechanobiological aetiopathogenesis of tendinopathy: is it the over-stimulation or the under-stimulation of tendon cells? Int J Exp Pathol 88(4):217–226

14. Arnoczky SP, Lavagnino M, Whallon JH, Hoonjan A (2002) In situ cell nucleus deformation in tendons under tensile load; a morphological analysis using confocal laser microscopy. J Orthop Res 20(1):29–35

15. Bailey AJ (2001) Molecular mechanisms of ageing in connective tissues. Mech Ageing Dev 122(7):735–755

16. Barber-Westin SD, Noyes FR (2011) Factors used to determine return to unrestricted sports activities after anterior cruciate ligament reconstruction. Arthroscopy 27(12): 1697–1705

17. Barber-Westin SD, Noyes FR (2011) Objective criteria for return to athletics after anterior cruciate ligament reconstruction and subsequent reinjury rates: a systematic review. Phys Sportsmed 39(3):100–110

18. Barenius B, Ponzer S, Shalabi A, Bujak R, Norlen L, Eriksson K (2014) Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. Am J Sports Med 42(5):1049–1057

19. Barnard K, Light ND, Sims TJ, Bailey AJ (1987) Chemistry of the collagen cross-links. Origin and partial characterization of a putative mature cross-link of collagen. Biochem J 244(2):303–309

20. Batista F, Nery C, Pinzur M, Monteiro AC, de Souza EF, Felippe FH, Alcantara MC, Campos RS (2008) Achilles tendinopathy in diabetes mellitus. Foot Ankle Int 29(5):498–501

21. Beynnon BD, Fleming BC, Johnson RJ, Nichols CE, Renstrom PE, Pope MH (1995) Anterior cruciate ligament strain behavior during rehabilitation exercises in vivo... p resented at the joint meeting of the International Society of the Knee/International Arthroscopy Association of America, Copenhagen, Denmark, June 27, 1993. Am J Sports Med 23(1):24–34

22. Beynnon BD, Johnson RJ, Fleming BC, Stankewich CJ, Renstrom PA, Nichols CE (1997) The strain behavior of the anterior cruciate ligament during squatting and active flexion-extension: a comparison of an open and a closed kinetic chain exercise. Am J Sports Med 25(6):823–829

23. Beynnon BD, Johnson RJ, Naud S, Fleming BC, Abate JA, Brattbakk B, Nichols CE (2011) Accelerated versus nonaccelerated rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind investigation evaluating knee joint laxity using roentgen stereophotogrammetric analysis. Am J Sports Med 39(12):2536–2548

24. Biggs A, Jenkins WL, Urch SE, Shelbourne KD (2009) Rehabilitation for patients following ACL reconstruction: a knee symmetry model. N Am J Sports Phys Ther 4(1):2–12

25. Bosch F (2010) Krachttraining en coördinatie. Een integratieve benadering. 2010 Uitgevers, Rotterdam.

26. Branch T, Stinton S, Sternberg M, Hutton W, Lavoie F, Guier C, Neyret P (2015) Robotic axial lower leg testing: repeatability and reproducibility. Knee Surg Sports Traumatol Arthrosc 23(10):2892–2899

27. Chbinou N, Frenette J (2004) Insulin-dependent diabetes impairs the inflammatory response and delays angiogenesis following Achilles tendon injury. Am J Physiol Regul Integr Comp Physiol 286(5):R952–957

28. Christensen JC, Goldfine LR, West HS (2013) The effects of early aggressive rehabilitation on outcomes after anterior cruciate ligament reconstruction using autologous hamstring tendon: a randomized clinical trial. J Sport Rehabil 22(3):191–201

29. Claes S, Verdonk P, Forsyth R, Bellemans J (2011) The "ligamentization" process in anterior cruciate ligament reconstruction: what happens to the human graft? A systematic review of the literature. Am J Sports Med 39(11):2476–2483

30. Clatworthy MG, Annear P, Bulow JU, Bartlett RJ (1999) Tunnel widening in anterior cruciate ligament reconstruction: a prospective evaluation of hamstring and patella tendon grafts. Knee Surg Sports Traumatol Arthrosc 7(3):138–145

31. Collins M, Raleigh SM (2009) Genetic risk factors for musculoskeletal soft tissue injuries. Med Sport Sci 54:136–149

32. Cook JL, Purdam CR (2009) Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. Br J Sports Med 43(6):409–416

33. Creighton DW, Shrier I, Shultz R, Meeuwisse WH, Matheson GO (2010) Return-to-play in sport: a decision-based model. Clin J Sport Med 20(5):379–385

34. De Carlo M, Klootwyk TE, Shelbourne KD (1997) ACL surgery and accelerated rehabilitation: revisited. J Sport Rehabil 6(2):144–156

35. de Mos M, van El B, DeGroot J, Jahr H, van Schie HT, van Arkel ER, Tol H, Heijboer R, van Osch GJ, Verhaar JA (2007) Achilles tendinosis: changes in biochemical composition and collagen turnover rate. Am J Sports Med 35(9):1549–1556

36. Di Stasi SL, Snyder-Mackler L (2012) The effects of neuromuscular training on the gait patterns of ACL-deficient men and women. Clin Biomech (Bristol, Avon) 27(4):360–365

37. Docking SI, Rosengarten SD, Daffy J, Cook JL (2014) Treat the donut, not the hole: The pathological Achilles and patellar tendon has sufficient amounts of normal tendon structure. J Sc Med Sport 18:e2

38. Dunn WR, Spindler KP, Consortium M (2010) Predictors of activity level 2 years after anterior cruciate ligament reconstruction (ACLR): a Multicenter Orthopaedic Outcomes Network (MOON) ACLR cohort study. Am J Sports Med 38(10):2040–2050

39. Eitzen I, Holm I, Risberg MA (2009) Preoperative quadriceps strength is a significant predictor of knee function two years after anterior cruciate ligament reconstruction. Br J Sports Med 43(5):371–376

40. Engelen-van Melick N, van Cingel RE, Tijssen MP, Nijhuis-van der Sanden MW (2013) Assessment of functional performance after anterior cruciate ligament reconstruction: a systematic review of measurement procedures. Knee Surg Sports Traumatol Arthrosc 21(4):869–879

41. Engelen-van Melick N, Cingel van RE, Tienen van TG, Nijhuis-van der Sanden MW (2015) Functional performance 2-9 years after ACL reconstruction. Cross-section al comparison betwen athletes with bone-patellar tendon-bone, semitendinosus/gracilis and healthy controls. Knee Surg Sports Traumatol Arthrosc Sep 24 [Epub ahead of print]

42. Engelen-van Melick N HW, Brooijmans F, Hendriks EJ, Neeter C, Van Tienen TG, Van Cingel RE (De Gans;Amersfoort (2014) KNGF Evidence Statement Revalidatie na voorste-kruisbandreconstructie

43. Escamilla RF, Macleod TD, Wilk KE, Paulos L, Andrews JR (2012) Anterior cruciate ligament strain and tensile forces for weight-bearing and non-weight-bearing exercises: a guide to exercise selection. J Orthop & Sports Phys Ther 42(3):208-220

44. Evans S, Shaginaw J, Bartolozzi A (2014) Acl reconstruction - it's all about timing. Int J Sports Phys Ther 9(2):268-273

45. Everhart JS, Best TM, Flanigan DC (2015) Psychological predictors of anterior cruciate ligament reconstruction outcomes: a systematic review. Knee Surg Sports Traumatol Arthrosc 23(3):752-762

46. Faunø P, Rahr-Wagner L, Lind M (2014) Risk for Revision After Anterior Cruciate Ligament Reconstruction Is Higher Among Adolescents: Results From the Danish Registry of Knee Ligament Reconstruction. Orthop J Sports Med 2(10):1-7

47. Feller J, Webster KE (2013) Return to sport following anterior cruciate ligament reconstruction. Int Orthop 37(2):285-290

48. Fredberg U, Stengaard-Pedersen K (2008) Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation. Scand J Med Sci Sports 18(1):3-15

49. Fu SC, Rolf C, Cheuk YC, Lui PP, Chan KM (2010) Deciphering the pathogenesis of tendinopathy: a three-stages process. Sports Med Arthrosc Rehabil Ther Technol 2:30

50. Gisslen K, Alfredson H (2005) Neovascularisation and pain in jumper's knee: a prospective clinical and sonographic study in elite junior volleyball players. Br J Sports Med 39(7):423-428; discussion 423-428

51. Gokeler A, Benjaminse A, van Eck CF, Webster KE, Schot L, Otten E (2013) Return of normal gait as an outcome measurement in acl reconstructed patients. A systematic review. Int J Sports Phys Ther 8(4):441-451

52. Gokeler A, Bisschop M, Benjaminse A, Myer GD, Eppinga P, Otten E (2014) Quadriceps function following ACL reconstruction and rehabilitation: implications for optimisation of current practices. Knee Surg Sports Traumatol Arthrosc 22(5):1163-1174

53. Gokeler A, Benjaminse A, Welling W, Alferink M, Eppinga P, Otten B (2015) The effects of attentional focus on jump performance and knee joint kinematics in patients after ACL reconstruction. Phys Ther Sport 16(2):114-120

54. Gokeler A, Benjaminse A, Hewett TE, Paterno MV, Ford KR, Otten E, Myer GD (2013) Feedback techniques to target functional deficits following anterior cruciate ligament reconstruction: implications for motor control and reduction of second injury risk. Sports Med 43(11):1065-1074

55. Gokeler A, Eppinga P, Dijkstra PU, Welling W, Padua DA, Otten E, Benjaminse A (2014) Effect of fatigue on landing performance assessed with the landing error scoring system (less) in patients after ACL reconstruction. A pilot study. Int J Sports Phys Ther 9(3):302-311

56. Gokeler A, Benjaminse A, Hewett TE, Lephart SM, Engebretsen L, Ageberg E, Engelhardt M, Arnold MP, Postema K, Otten E, Dijkstra PU (2012) Proprioceptive deficits after ACL injury: are they clinically relevant? Br J Sports Med 46(3):180-192

57. Goncalves-Neto J, Witzel SS, Teodoro WR, Carvalho-Junior AE, Fernandes TD, Yoshinari HH (2002) Changes in collagen matrix composition in human posterior tibial tendon dysfunction. Joint Bone Spine 69(2):189-194

58. Grant WP, Sullivan R, Sonenshine DE, Adam M, Slusser JH, Carson KA, Vinik AI (1997) Electron microscopic investigation of the effects of diabetes mellitus on the Achilles tendon. J Foot Ankle Surg 36(4):272-278; discussion 330

59. Grindem H, Granan LP, Risberg MA, Engebretsen L, Snyder-Mackler L, Eitzen I (2015) How does a combined preoperative and postoperative rehabilitation programme influence the outcome of ACL reconstruction 2 years after surgery? A comparison between patients in the Delaware-Oslo ACL Cohort and the Norwegian National Knee Ligament Registry. Br J Sports Med 49(6):385-389

60. Guenther D, Griffith C, Lesniak B, Lopomo N, Grassi A, Zaffagnini S, Fu FH, Musahl V (2015) Anterolateral rotatory instability of the knee. Knee Surg Sports Traumatol Arthrosc 23(10):2909-2917

61. Han DL, Nyland J, Kendzior M, Nawab A, Caborn DN (2012) Intratunnel versus extratunnel fixation of hamstring autograft for anterior cruciate ligament reconstruction. Arthroscopy 28(10):1555-1566

62. Hansen M, Miller BF, Holm L, Doessing S, Petersen SG, Skovgaard D, Frystyk J, Flyvbjerg A, Koskinen S, Pingel J, Kjaer M, Langberg H (2009) Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. J Appl Physiol (1985) 106(4):1435-1443

63. Hansen M, Kongsgaard M, Holm L, Skovgaard D, Magnusson SP, Qvortrup K, Larsen JO, Aagaard P, Dahl M, Serup A, Frystyk J, Flyvbjerg A, Langberg H, Kjaer M (2009) Effect of estrogen on tendon collagen synthesis, tendon structural characteristics, and biomechanical properties in postmenopausal women. J Appl Physiol (1985) 106(4):1385-1393

64. Harput G, Kilinc HE, Ozer H, Baltaci G, Mattacola CG (2015) Quadriceps and hamstring strength recovery during early period of neuromuscular rehabilitation following ACL hamstring tendon autograft reconstruction. J Sport Rehabil Aug 26 [Epub ahead of print]

65. Harris JD, Abrams GD, Bach BR, Williams D, Heidloff D, Bush-Joseph CA, Verma NN, Forsythe B, Cole BJ (2014) Return to sport after ACL reconstruction. Orthopedics 37(2):e103-108

66. Hartigan EH, Lynch AD, Logerstedt DS, Chmielewski TL, Snyder-Mackler L (2013) Kinesiophobia after anterior cruciate ligament rupture and reconstruction: noncopers versus potential copers. J Orthop Sports Phys Ther 43(11):821-832

67. Heijne A, Werner S (2007) Early versus late start of open kinetic chain quadriceps exercises after ACL reconstruction with patellar tendon or hamstring grafts: a prospective randomized outcome study. Knee Surg Sports Traumatol Arthrosc 15(4):402-414

68. Heinemeier KM, Olesen JL, Haddad F, Langberg H, Kjaer M, Baldwin KM, Schjerling P (2007) Expression of collagen and related growth factors in rat tendon and skeletal muscle in response to specific contraction types. J Physiol 582(3):1303-1316

69. Herbst E, Hoser C, Hildebrandt C, Raschner C, Hepperger C, Pointner H, Fink C (2015) Functional assessments for decision-making regarding return to sports following ACL reconstruction. Part II: clinical application of a new test battery. Knee Surg Sports Traumatol Arthrosc 23(5):1283-1291

70. Hiemstra LA, Webber S, MacDonald PB, Kriellaars DJ (2007) Contralateral limb strength deficits after anterior cruciate ligament reconstruction using a hamstring tendon graft. Clin Biomech (Bristol, Avon) 22(5):543-550

71. Hill GN, O'Leary ST (2013) Anterior cruciate ligament reconstruction: the short-term recovery using the Knee Injury and Osteoarthritis Outcome Score (KOOS). Knee Surg Sports Traumatol Arthrosc 21(8):1889-1894

72. Holmes GB, Lin J (2006) Etiologic factors associated with symptomatic achilles tendinopathy. Foot Ankle Int 27(11):952-959

73. Howell SM, Taylor MA (1996) Brace-free rehabilitation, with early return to activity, for knees reconstructed with a double-looped semitendinosus and gracilis graft. J Bone Joint Surg Am 78(6):814-825

74. Howell SM, Hull ML (1998) Aggressive rehabilitation using hamstring tendons: graft construct, tibial tunnel placement, fixation properties, and clinical outcome. Am J Knee Surg 11(2):120-127

75. Howell SM, Smith C, Hull ML (2009) Management of a patient with an anterior cruciate ligament rupture. Operative Techniques in Sports Medicine 17(1):39-46

76. Howell SM, Knox KE, Farley TE, Taylor MA (1995) Revascularization of a human anterior cruciate ligament graft during the first two years of implantation. Am J Sports Med 23(1):42-49

77. Howell SM, Wallace MP, Hull ML, Deutsch ML (1999) Evaluation of the single-incision arthroscopic technique for anterior cruciate ligament replacement. A study of tibial tunnel placement, intraoperative graft tension, and stability. Am J Sports Med 27(3):284-293

78. Hulzebos EH, Smit Y, Helders PP, van Meeteren NL (2012) Preoperative physical therapy for elective cardiac surgery patients. Cochrane Database Syst Rev 11:CD010118

79. Hurd WJ, Axe MJ, Snyder-Mackler L (2008) Influence of age, gender, and injury mechanism on the development of dynamic knee stability after acute ACL rupture. J Orthop Sports Phys Ther 38(2):36-41

80. Hurd WJ, Axe MJ, Snyder-Mackler L (2008) A 10-year prospective trial of a patient management algorithm and screening examination for highly active individuals with anterior cruciate ligament injury: Part 1, outcomes. Am J Sports Med 36(1):40-47

81. Janssen RP, Scheffler SU (2014) Remodeling of hamstring tendon grafts after ACL reconstruction. In: Siebold R, Dejour D, Zaffagnini S (eds) Anterior Cruciate Ligament Reconstruction-A Practical Surgical Guide. Springer

82. Janssen RP, Scheffler SU (2014) Intra-articular remodelling of hamstring tendon grafts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 22(9):2102-2108

83. Janssen RP, Scheffler SU (2016) Graft remodeling & ligamentization after ACL reconstruction. In: Prodromos CC (ed) The Anterior Cruciate Ligament. Reconstruction and Basic Science. 2nd edn. Saunders, an imprint of Elsevier, Inc

84. Janssen RP, Velden van der MJ, Pasmans HL, Sala HA (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21(4):898-905

85. Janssen RP, van der Velden MJ, van den Besselaar M, Reijman M (2015) Prediction of length and diameter of hamstring tendon autografts for knee ligament surgery in Caucasians. Knee Surg Sports Traumatol Arthrosc Jun 28 [Epub ahead of print]

86. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM (2013) Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. Knee Surg Sports Traumatol Arthrosc 21(9):1977-1988

87. Janssen RP, Engelen-van Melick N, Mourik van JB, Reijman M, Rhijn van LW (2015) Anterior cruciate ligament reconstruction and accelerated brace-free rehabilitation: a systematic review. Part I. Hamstring tendon autograft. Eur J Phys Rehabil Med (Under review)

88. Janssen RP, Wijk van der J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(8):1299-1306

89. Jarvinen M, Jozsa L, Kannus P, Jarvinen TL, Kvist M, Leadbetter W (1997) Histopathological findings in chronic tendon disorders. Scand J Med Sci Sports 7(2):86-95

90. Kadler KE, Holmes DF, Trotter JA, Chapman JA (1996) Collagen fibril formation. Biochem J 316 (Pt 1):1-11

91. Kelso JAS (1995) Dynamic patterns: The self organization of brain and behavior. Cambridge MA: MIT Press

92. Kinikli GI, Yuksel I, Baltaci G, Atay OA (2014) The effect of progressive eccentric and concentric training on functional performance after autogenous hamstring anterior cruciate ligament reconstruction: a randomized controlled study. Acta Orthop Traumatol Turc 48(3):283-289

93. Kjaer M, Langberg H, Magnusson P (2003) [Overuse injuries in tendon tissue: insight into adaptation mechanisms]. Ugeskr Laeger 165(14):1438-1443

94. Knobloch K, Kraemer R, Lichtenberg A, Jagodzinski M, Gossling T, Richter M, Zeichen J, Hufner T, Krettek C (2006) Achilles tendon and paratendon microcirculation in midportion and insertional tendinopathy in athletes. Am J Sports Med 34(1):92-97

95. Kousa P, Slauterbeck JR, Beynnon BD (2008) Anterior cruciate ligament strain behavior during rehabilitation exercises. In: Prodromos CC (ed) The Anterior Cruciate Ligament. Reconstruction and Basic Science. Saunders by Elsevier, Inc

96. Kruse LM, Gray B, Wright RW (2012) Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. J Bone Joint Surg Am 94(19):1737-1748

97. Lawhorn KW, Howell SM (2007) Principles for using hamstring tendons for anterior cruciate ligament reconstruction. Clin Sports Med 26(4):567-585

98. Lepley LK, Palmieri-Smith R (2013) Effect of eccentric strengthening after anterior cruciate ligament reconstruction on quadriceps strength. J Sport Rehabil 22(2):150-156

99. Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ (2011) Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. Am J Sports Med 39(12):2595-2603

100. Lynch HA, Johannessen W, Wu JP, Jawa A, Elliott DM (2003) Effect of fiber orientation and strain rate on the nonlinear uniaxial tensile material properties of tendon. J Biomech Eng 125(5):726-731

101. Maffulli N, Khan KM, Puddu G (1998) Overuse tendon conditions: time to change a confusing terminology. Arthroscopy 14(8):840-843

102. Magnusson SP, Langberg H, Kjaer M (2010) The pathogenesis of tendinopathy: balancing the response to loading. Nat Rev Rheumatol 6(5):262-268

103. Majima T, Yasuda K, Tago H, Tanabe Y, Minami A (2002) Rehabilitation after hamstring anterior cruciate ligament reconstruction. Clin Orthop Relat Res (397):370-380

104. McLoughlin RF, Raber EL, Vellet AD, Wiley JP, Bray RC (1995) Patellar tendinitis: MR imaging features, with suggested pathogenesis and proposed classification. Radiology 197(3):843-848

105. Menetrey J, Duthon VB, Laumonier T, Fritschy D (2008) "Biological failure" of the anterior cruciate ligament graft. Knee Surg Sports Traumatol Arthrosc 16(3):224-231

106. Middleton KK, Hamilton T, Irrgang JJ, Karlsson J, Harner CD, Fu FH (2014) Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1. Knee Surg Sports Traumatol Arthrosc 22(7):1467-1482

107. Miller BF, Hansen M, Olesen JL, Schwarz P, Babraj JA, Smith K, Rennie MJ, Kjaer M (2007) Tendon collagen synthesis at rest and after exercise in women. J Appl Physiol (1985) 102(2):541-546

108. Miller BF, Hansen M, Olesen JL, Flyvbjerg A, Schwarz P, Babraj JA, Smith K, Rennie MJ, Kjaer M (2006) No effect of menstrual cycle on myofibrillar and connective tissue protein synthesis in contracting skeletal muscle. Am J Physiol Endocrinol Metab 290(1):E163-E168

109. Millett PJ, Wickiewicz TL, Warren RF (2001) Motion loss after ligament injuries to the knee. Part II: prevention and treatment. Am J Sports Med 29(6):822-828

110. Mohtadi N, Chan D, Barber R, Paolucci EO (2015) Reruptures, reinjuries, and revisions at a minimum 2-year follow-up: a randomized clinical trial comparing 3 graft types for ACL reconstruction. Clin J Sport Med Jun 29 [Epub ahead of print]

111. Movin T, Kristoffersen-Wiberg M, Rolf C, Aspelin P (1998) MR imaging in chronic Achilles tendon disorder. Acta Radiol 39(2):126-132

112. Movin T, Kristoffersen-Wiberg M, Shalabi A, Gad A, Aspelin P, Rolf C (1998) Intratendinous alterations as imaged by ultrasound and contrast medium-enhanced magnetic resonance in chronic achillodynia. Foot Ankle Int 19(5):311-317

113. Muller B, Bowman KF, Jr., Bedi A (2013) ACL graft healing and biologics. Clin Sports Med 32(1):93-109

114. Muller SA, Todorov A, Heisterbach PE, Martin I, Majewski M (2015) Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. Knee Surg Sports Traumatol Arthrosc 23(7):2097-2105

115. Nakama LH, King KB, Abrahamsson S, Rempel DM (2005) Evidence of tendon microtears due to cyclical loading in an in vivo tendinopathy model. J Orthop Res 23(5):1199-1205

116. Nguyen DT (2015) Anterior cruciate ligament 3-D fiber anatomy, fluorescence arthroscopy & healing. Universiteit van Amsterdam, Amsterdam

117. Nishio Y, Majima T, Tago H, Yasuda K, Kaneda K (1997) Limit and effects of accelerated rehabilitation after anterior cruciate ligament reconstruction. Hokkaido Journal of Orthopedic and Traumatic Surgery 40(1):12-16

118. Nyland J, Brand E, Fisher B (2010) Update on rehabilitation following ACL reconstruction. Open Access J Sports Med 1:151-166

119. Ohberg L, Lorentzon R, Alfredson H (2001) Neovascularisation in Achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation. Knee Surg Sports Traumatol Arthrosc 9(4):233-238

120. Oiestad BE, Engebretsen L, Storheim K, Risberg MA (2009) Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med 37(7):1434-1443

121. Oiestad BE, Holm I, Gunderson R, Myklebust G, Risberg MA (2010) Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? Arthritis Care Res (Hoboken) 62(12):1706-1714

122. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM (1995) Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 38(8):1134-1141

123. Oosting E, Jans MP, Dronkers JJ, Naber RH, Dronkers-Landman CM, Appelman-de Vries SM, van Meeteren NL (2012) Preoperative home-based physical therapy versus usual care to improve functional health of frail older adults scheduled for elective total hip arthroplasty: a pilot randomized controlled trial. Arch Phys Med Rehabil 93(4):610-616

124. Paterno MV (2015) Incidence and predictors of second anterior cruciate ligament injury after primary reconstruction and return to sport. J Athl Train Sep 4 [Epub ahead of print]

125. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE (2012) Incidence of contralateral and ipsilateral anterior cruciate ligament (ACL) injury after primary ACL reconstruction and return to sport. Clin J Sport Med 22(2):116-121

126. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE (2014) Incidence of second ACL injuries 2 years after primary ACL reconstruction and return to sport. Am J Sports Med 42(7):1567–1573

127. Paterno MV, Schmitt LC, Ford KR, Rauh MJ, Myer GD, Huang B, Hewett TE (2010) Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport. Am J Sports Med 38(10):1968–1978

128. Pauzenberger L, Syre S, Schurz M (2013) "Ligamentization" in hamstring tendon grafts after anterior cruciate ligament reconstruction: a systematic review of the literature and a glimpse into the future. Arthroscopy 29(10):1712–1721

129. Pinczewski LA, Deehan DJ, Salmon LJ, Russell VJ, Clingeleffer A (2002) A five-year comparison of patellar tendon versus four-strand hamstring tendon autograft for arthroscopic reconstruction of the anterior cruciate ligament. Am J Sports Med 30(4):523–536

130. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J (2007) A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. Am J Sports Med 35(4):564–574

131. Pufe T, Petersen WJ, Mentlein R, Tillmann BN (2005) The role of vasculature and angiogenesis for the pathogenesis of degenerative tendons disease. Scand J Med Sci Sports 15(4):211–222

132. Renstrom PA (2013) Eight clinical conundrums relating to anterior cruciate ligament (ACL) injury in sport: recent evidence and a personal reflection. Br J Sports Med 47(6):367–372

133. Riley G (2008) Tendinopathy–from basic science to treatment. Nat Clin Pract Rheumatol 4(2):82–89

134. Riley GP (2005) Gene expression and matrix turnover in overused and damaged tendons. Scand J Med Sci Sports 15(4):241–251

135. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL (1994) Tendon degeneration and chronic shoulder pain: changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. Ann Rheum Dis 53(6):359–366

136. Risberg MA, Holm I, Myklebust G, Engebretsen L (2007) Neuromuscular training versus strength training during first 6 months after anterior cruciate ligament reconstruction: a randomized clinical trial. Phys Ther 87(6):737–750

137. Ryan J, Magnussen RA, Cox CL, Hurbanek JG, Flanigan DC, Kaeding CC (2014) ACL reconstruction: do outcomes differ by sex? A systematic review. J Bone Joint Surg Am 96(6):507–512

138. Sakata T, Wang Y, Halloran BP, Elalieh HZ, Cao J, Bikle DD (2004) Skeletal unloading induces resistance to insulin-like growth factor-I (IGF-I) by inhibiting activation of the IGF-I signaling pathways. J Bone Miner Res 19(3):436–446

139. Sandon A, Werner S, Forssblad M (2015) Factors associated with returning to football after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 23(9):2514–2521

140. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16(9):834–842

141. Schie van HT, Docking SI, Daffy J, Preat SE, Rosengarten S, Cook JL (2013) Ultrasound tissue characteriziation, an innovative technique for injury-prevention and monitoring of tendinopathy. Br J Sports Med 47:e2

142. Schizas N, Weiss R, Lian O, Frihagen F, Bahr R, Ackermann PW (2012) Glutamate receptors in tendinopathic patients. J Orthop Res 30(9):1447–1452

143. Schmitt LC, Paterno MV, Hewett TE (2012) The impact of quadriceps femoris strength asymmetry on functional performance at return to sport following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 42(9):750–759

144. Schroeder MJ, Krishnan C, Dhaher YY (2015) The influence of task complexity on knee joint kinetics following ACL reconstruction. Clin Biomech (Bristol, Avon) 30(8):852–859

145. Screen HR, Lee DA, Bader DL, Shelton JC (2004) An investigation into the effects of the hierarchical structure of tendon fascicles on micromechanical properties. Proc Inst Mech Eng H 218(2):109–119

146. Sena MP, DellaMaggioria R, Lotz JC, Feeley BT (2015) A mechanical pivot-shift device for continuously applying defined loads to cadaveric knees. Knee Surg Sports Traumatol Arthrosc 23(10):2900–2908

147. September AV, Schwellnus MP, Collins M (2007) Tendon and ligament injuries: the genetic component. Br J Sports Med 41(4):241–246; discussion 246

148. Shaarani SR, O'Hare C, Quinn A, Moyna N, Moran R, O'Byrne JM (2013) Effect of prehabilitation on the outcome of anterior cruciate ligament reconstruction. Am J Sports Med 41(9):2117–2127

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

150. Shelbourne KD, Gray T (1997) Anterior cruciate ligament reconstruction with autogenous patellar tendon graft followed by accelerated rehabilitation. A two- to nine-year follow-up. Am J Sports Med 25(6):786–795

151. Shelbourne KD, Gray T (2000) Results of anterior cruciate ligament reconstruction based on meniscus and articular cartilage status at the time of surgery. Five- to fifteen-year evaluations. Am J Sports Med 28(4):446–452

152. Shelbourne KD, Klotz C (2006) What I have learned about the ACL: utilizing a progressive rehabilitation scheme to achieve total knee symmetry after anterior cruciate ligament reconstruction. J Orthop Sci 11(3):318–325

153. Shelbourne KD, Vanadurongwan B, Gray T (2007) Primary anterior cruciate ligament reconstruction using contralateral patellar tendon autograft. Clin Sports Med 26(4):549–565

154. Stoehr A, Mayr H, Wondrasch B, Fink C (2014) Rehabilitation and return to sports. In: Siebold R, Dejour D, Zaffagnini S (eds) Anterior Cruciate Ligament Reconstruction–A Practical Surgical Guide. Springer

155. The Swedish National Knee Ligament Register. Swedish ACL register: annual report 2011.

156. Terslev L, Qvistgaard E, Torp-Pedersen S, Laetgaard J, Danneskiold-Samsoe B, Bliddal H (2001) Ultrasound and Power Doppler findings in jumper's knee – preliminary observations. Eur J Ultrasound 13(3):183–189

157. Thomee R, Kaplan Y, Kvist J, Myklebust G, Risberg MA, Theisen D, Tsepis E, Werner S, Wondrasch B, Witvrouw E (2011) Muscle strength and hop performance criteria prior to return to sports after ACL reconstruction. Knee Surg Sports Traumatol Arthrosc 19(11):1798–1805

158. Thorpe CT, Stark RJ, Goodship AE, Birch HL (2010) Mechanical properties of the equine superficial digital flexor tendon relate to specific collagen cross-link levels. Equine Vet J Suppl(38):538–543

159. Thorpe CT, Streeter I, Pinchbeck GL, Goodship AE, Clegg PD, Birch HL (2010) Aspartic acid racemization and collagen degradation markers reveal an accumulation of damage in tendon collagen that is enhanced with aging. J Biol Chem 285(21):15674–15681

160. Tohyama H, Yoshikawa T, Ju YJ, Yasuda K (2009) Revascularization in the tendon graft following anterior cruciate ligament reconstruction of the knee: its mechanisms and regulation. Chang Gung Med J 32(2):133–139

161. Twigg SM, Chen MM, Joly AH, Chakrapani SD, Tsubaki J, Kim HS, Oh Y, Rosenfeld RG (2001) Advanced glycosylation end products up-regulate connective tissue growth factor (insulin-like growth factor-binding protein-related protein 2) in human fibroblasts: a potential mechanism for expansion of extracellular matrix in diabetes mellitus. Endocrinology 142(5):1760–1769

162. Vadala A, Iorio R, De Carli A, Argento G, Di Sanzo V, Conteduca F, Ferretti A (2007) The effect of accelerated, brace free, rehabilitation on bone tunnel enlargement after ACL reconstruction using hamstring tendons: a CT study. Knee Surg Sports Traumatol Arthrosc 15(4):365–371

163. Vairo GL, McBrier NM, Miller SJ, Buckley WE (2010) Premature knee osteoarthritis after anterior cruciate ligament reconstruction dependent on autograft. J Sport Rehabil 19(1):86–97

164. van der Sluis G, Goldbohm RA, Bimmel R, Garre FG, Elings J, Hoogeboom TJ, van Meeteren NL (2015) What augmented physical activity and empowerment can bring to patients receiving total knee replacement: content, implementation, and comparative effectiveness of a new function-tailored care pathway in a routine care setting. Biomed Res Int 2015:745864

165. van Grinsven S, van Cingel RE, Holla CJ, van Loon CJ (2010) Evidence-based rehabilitation following anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 18(8):1128–1144

166. van Meer BL, Waarsing JH, van Eijsden WA, Meuffels DE, van Arkel ER, Verhaar JA, Bierma-Zeinstra SM, Reijman M (2014) Bone mineral density changes in the knee following anterior cruciate ligament rupture. Osteoarthritis Cartilage 22(1):154–161

167. Walden M, Hagglund M, Magnusson H, Ekstrand J (2011) Anterior cruciate ligament injury in elite football: a prospective three-cohort study. Knee Surg Sports Traumatol Arthrosc 19(1):11-19

168. Warner SJ, Smith MV, Wright RW, Matava MJ, Brophy RH (2011) Sport-specific outcomes after anterior cruciate ligament reconstruction. Arthroscopy 27(8): 1129-1134

169. Webster KE, Austin DC, Feller JA, Clark RA, McClelland JA (2015) Symmetry of squatting and the effect of fatigue following anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 23(11):3208-3213

170. Wilk KE, Reinold MM, Hooks TR (2003) Recent advances in the rehabilitation of isolated and combined anterior cruciate ligament injuries. Orthop Clin North Am 34(1):107-137

171. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part I: continuous passive motion, early weight bearing, postoperative bracing, and home-based rehabilitation. J Knee Surg 21(3):217-224

172. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part II: open versus closed kinetic chain exercises, neuromuscular electrical stimulation, accelerated rehabilitation, and miscellaneous topics. J Knee Surg 21(3):225-234

173. Xergia SA, McClelland JA, Kvist J, Vasiliadis HS, Georgoulis AD (2011) The influence of graft choice on isokinetic muscle strength 4-24 months after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19(5):768-780

174. Xie X, Xiao Z, Li Q, Zhu B, Chen J, Chen H, Yang F, Chen Y, Lai Q, Liu X (2015) Increased incidence of osteoarthritis of knee joint after ACL reconstruction with bone-patellar tendon-bone autografts than hamstring autografts: a meta-analysis of 1,443 patients at a minimum of 5 years. Eur J Orthop Surg Traumatol 25(1):149-159

175. Yabroudi MA, Irrgang JJ (2013) Rehabilitation and return to play after anatomic anterior cruciate ligament reconstruction. Clin Sports Med 32(1):165-175

176. Zabala ME, Favre J, Scanlan SF, Donahue J, Andriacchi TP (2013) Three-dimension al knee moments of ACL reconstructed and control subjects during gait, stair ascent, and stair descent. J Biomech 46(3):515-520

177. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Tsapralis K, Ricci M, Bragonzoni L, Della Villa S, Marcacci M (2014) Return to sport after anterior cruciate ligament reconstruction in professional soccer players. Knee 21(3):731-735

178. Zhu W, Wang D, Han Y, Zhang N, Zeng Y (2013) Anterior cruciate ligament (ACL) autograft reconstruction with hamstring tendons: clinical research among three rehabilitation procedures. Eur J Orthop Surg Traumatol 23(8):939-943

ENGLISH SUMMARY

Patients with an anterior cruciate ligament (ACL) rupture may experience knee instability and are at risk for concomitant injuries of menisci, cartilage and collateral ligaments. Functional instability of the knee can be treated by ACL reconstruction, which ranks number 6 of most performed orthopaedic operations.

The most recent incidence of ACL reconstructions in the Netherlands was estimated at 46 in 100.000 people per year. The incidence of ACL reconstructions increases, particularly in women as well as patients younger than 20 years and those above 40 years of age.

Hamstring tendons continue to gain in popularity as graft source for ACL reconstruction and success rate varies between 55-95%. Successful ACL reconstruction requires understanding of several factors: anatomical graft placement, mechanical properties of the selected graft tissue, mechanical behaviour and fixation strength of fixation materials as well as the biological processes that occur during graft healing. They influence directly the mechanical properties of the knee joint after ACL reconstruction and, therefore, determine the rehabilitation and time course until normal function of the knee joint can be expected.

The aim of this thesis is to gain insights into the characteristics and biology of hamstring tendons as well as long-term clinical outcome after hamstring tendon autograft ACL reconstruction with brace-free accelerated rehabilitation. The same surgical technique and standardized accelerated rehabilitation protocol were used in all clinical studies of this thesis.

Chapter 1 presents a historical perspective on ACL reconstruction with hamstring tendons and accelerated brace-free rehabilitation. Hamstrings tendon autograft ACL reconstructions have a 25-year track record. In the 1990's, advances in arthroscopic guides and better graft fixation techniques allowed single-incision ACL reconstruction with intra-articular drilling of the femoral tunnel. The 1990's were the decade of autograft transition from patellar tendon to hamstring tendon autografts in the Netherlands. Advocators argued that hamstring tendons were the preferred graft choice for ACL reconstruction because of superior strength, larger cross-sectional area for footprint recreation, graft tunnel conformity, biological incorporation, stability, and less donor site morbidity and anterior knee pain compared to bone-patellar tendon-bone autografts. Return to sports was allowed at 4-6 months after ACL reconstruction. As a result, this surgical reconstruction technique became popular in combination with accelerated brace-free rehabilitation protocols and is still widely used today.

A major challenge in postoperative rehabilitation after ACL reconstruction is optimizing the balance between muscular strengthening exercises and loading of the graft without compromising graft integrity. The research perspective on the topic is related to the aim of the thesis in this first chapter.

Chapter 2 presents an overview of the current knowledge on accelerated brace-free rehabilitation after ACL reconstruction with hamstring tendon autografts.
A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines from January 1, 1990 till December 31, 2014. The primary aim of this systematic review was to investigate the clinical outcome of accelerated brace-free rehabilitation after ACL reconstruction in adults. The secondary aims were the influence of accelerated rehabilitation on tunnel widening, tendon regeneration and time to return to sports after ACL reconstruction.

The results of the review showed that after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation: (1) anatomic reconstructions showed better results than nonanatomic reconstructions; (2) there was no difference between single- and double-bundle reconstructions; (3) gender and age did not influence clinical outcome; (4) femoral and tibial tunnel widening occurred; (5) early start of open kinetic exercises at 4 weeks in a limited range of motion (90°-45°) and progressive concentric and eccentric exercises from 12 weeks did not alter outcome; (6) Nintendo Wii® activities could address physical therapy goals; (7) hamstring tendons regenerated after harvest and (8) biological knowledge did not support return to sports at 4-6 months.

In conclusion, accelerated brace-free rehabilitation may contribute to successful ACL reconstruction with hamstring tendon autograft in adult patients of all ages and gender. Further research is necessary to define the optimal balance of graft loading and graft healing in the various rehabilitation phases after ACL reconstruction as well as the development of valid, criterion-based assessments to determine customized phases of rehabilitation and readiness for sport-specific training and return to play.

In the next four chapters, I have chosen to deepen the knowledge on hamstring tendon autografts used for ACL reconstruction. These chapters encompass the central part of the thesis and focus on hamstring tendon graft size, regeneration, biology and remodelling of human hamstring tendon autografts.

Prediction of hamstring tendon graft size could facilitate preoperative planning of knee ligament surgery and may reduce the need for allografts in complex knee reconstructions. This reduces surgical costs and increases the quality of ligament reconstructions with regard to possible graft rupture and postoperative stability.
The aim of **Chapter 3** was to analyse whether length and diameter of hamstring tendon autografts can be predicted preoperatively with anthropometric parameters and patient characteristics. In this observational study, 725 consecutive Caucasian patients scheduled for ACL reconstruction were included. Preoperatively patient gender, age, height and weight were recorded. After harvest, tendon lengths of both the gracilis and semitendinosus tendons were measured. The diameter of the final 4-strand hamstring tendon autograft was recorded. The relationship between length and diameter of the tendon grafts and different anthropometric parameters were assessed by linear and logistic regression analyses.

The results showed that the mean lengths of the semitendinosus and gracilis tendon autografts were 28.9 ± 3.1 and 27.7 ± 3.0 cm, respectively. Two patients (0.3%) had a semitendinosus tendon length shorter than 21 cm. Twelve patients (1.7%) had gracilis tendons shorter than 21 cm. A total of 42 patients (5.8%) had graft diameters ≤ 7 mm, 359 patients (49.7%) had graft diameters of 8 mm, and 322 patients (44.5%) diameters ≥ 9 mm. A correlation was found between gender and graft diameter < 8 mm. One in nine female patients had a diameter < 8 mm, the ratio in men was 1 in 36.

In conclusion, hamstring tendon autograft length and size can be predicted in Caucasians. Length of the gracilis and semitendinosus tendons was independently related to patient height. Smaller graft diameter was related to female gender.

Chapter 4 describes hamstring tendon regeneration in the upper leg after harvest for ACL reconstruction. Our hypothesis was that semitendinosus and gracilis tendons regenerate after harvest for ACL reconstruction and that isokinetic muscle strength is better restored in case of regeneration of hamstring tendons distal to the knee joint line.

Twenty-two patients scheduled for ACL reconstruction underwent prospective MRI analysis of both legs. The study consisted of 2 parts.
The first part was a prospective MRI study to determine the regeneration of semitendinosus and gracilis tendons after ACL reconstruction. Consecutive patients, who fulfilled the entry criteria as defined by the study protocol, underwent MRI of both legs preoperatively as well as 2 weeks, 6 and 12 months postoperatively. MRI parameters were tendon regeneration and morphology, muscle retraction and muscle cross-sectional area.
The second part was a prospective, double-blind study of isokinetic strength of quadriceps and hamstring muscles of both legs. Patients were examined preoperatively and 6 and 12 months postoperatively. Patients were evaluated by Tegner-, Lysholm- and International Knee Documentation Committee (IKDC) scores. Upper leg circumference measurements and KT-1000 laxity testing at 89 and 133 Newton (MEDmetric Co., San Diego, CA, USA) of both legs were performed.

The study showed that regeneration of the gracilis tendon after ACL reconstruction occurred in all patients. Regeneration of the semitendinosus tendon occurred in 14 patients. At 1 year, the surface area of the semitendinosus and gracilis muscles decreased compared to both preoperatively ($P < 0.01$) and the contralateral leg ($P < 0.01$). The cross-sectional area of the semitendinosus muscle decreased in the absence of tendon regeneration ($P = 0.05$). The cross-sectional area of the gracilis muscle was greater in case of regeneration distal to the joint line ($P = 0.01$). Muscle retraction of the semitendinosus muscle was increased in case of nonregeneration ($P = 0.02$).

We concluded that hamstring tendons regenerated after harvest of both semitendinosus and gracilis tendons for ACL reconstruction. Tendon regeneration was not associated with isokinetic flexion strength.

The in vivo human ACL graft biopsy study presented in **Chapter 5** illustrates the histology and morphology of hamstring tendon autograft remodelling in various phases after successful ACL reconstruction with standardized accelerated brace-free rehabilitation. It was a joint research project between Máxima Medical Centre (Eindhoven, The Netherlands) and Charité Centre for Musculoskeletal Surgery (Berlin, Germany). The hypothesis of the study was that hamstring tendon grafts undergo a remodelling process that will adapt its histological appearance to the morphology of the intact ACL and that this process is completed by one year.

Sixty-seven patients underwent retrieval of mid-substance biopsies after clinically successful hamstring tendon autograft ACL reconstruction. Samples were allocated to one of three groups depending on the time point of retrieval: group 1 (6–12 months; n = 15), group 2 (13–24 months; n = 16) and group 3 (>24 months; n = 11). Biopsies from native hamstring tendons (n = 17) and ACLs (n = 8) served as controls. Cellular density, vascular density, myofibroblast density and collagen fibril alignment were analysed by haematoxylin–eosin, Masson-Goldner-Trichrom and immunohistochemical staining protocols.

The study demonstrated that total cell number, compared with native hamstring tendon (330.4/mm^2), was increased in groups 1-3 (group 1 = 482.0/mm^2 ($P = 0.036$); group 2 = 850.9/mm^2 ($P = 0.005$); and group 3 = 595.6/mm^2 ($P = 0.043$)). There were no significant differences between the groups for vessel density. Myofibroblast density was higher in group 2 (199.6/mm^2) compared with native hamstring tendon (1.9/mm^2, $P = 0.014$). Myofibroblasts are known to be important cells during the healing of ACL grafts. Their appearance is typical for graft remodelling. The increasing myofibroblast density between 13 and 24 months indicated that the remodelling process in humans was prolonged compared with the results obtained in several animal studies. Collagen orientation was irregular up to 12 months. Thereafter, collagen orientation became more regular, adapting to, but not fully restoring, the appearance of the intact ACL. For the first 12 months, cells were predominantly ovoid. Ensuing cell morphology changed to spindle-shaped in group 2 and predominantly narrow long cells over 24 months.

In conclusion, human hamstring tendon grafts showed typical stages of graft remodelling, which was not completed up to 2 years after ACL reconstruction. The remodelling process in humans was prolonged compared with the results obtained in several animal studies.

Chapter 6 describes the current knowledge on hamstring tendon ACL graft remodelling. A comparison is made between human and animal data to discuss consequences for rehabilitation. A systematic review of the existing literature was performed between 1982 and 2012. Special focus was directed on in vivo human and animal studies analysing intra-articular tendon graft remodelling.

Animal and human in vitro and vivo research has demonstrated three characteristic stages of graft healing after ACL reconstruction: an early graft healing phase with central graft necrosis and hypocellularity and no detectable revascularization of the graft tissue, followed by a phase of proliferation, the time of most intensive remodelling and revascularization and finally, a ligamentization phase with characteristic restructuring of the graft towards the properties of the intact ACL. However, a full restoration of either the biological or biomechanical properties of the intact ACL was not achieved. Most importantly, the remodelling process in humans is prolonged compared to animal studies. While today's rehabilitation protocols are often extrapolated from findings in animal studies, current findings of human in vivo studies might require new postoperative regimens following hamstring tendon ACL reconstruction.

The long-term clinical and radiological outcome after hamstring tendon autograft ACL reconstruction with accelerated brace-free rehabilitation is presented in **Chapter 7**. Analysis was performed preoperatively and 10 years postoperatively in a prospective study of 100 patients. Clinical examination included Lysholm-, Tegner- and IKDC scores, KT-1000 testing and leg circumference measurements. Radiological evaluation included AP weight-bearing, lateral knee, Rosenberg and sky-view X-rays. Radiological classifications were according to Ahlbäck and Kellgren&Lawrence. Statistical analysis included univariate and multivariate logistic regressions.

The results showed a significant improvement ($P < 0.001$) between preoperative and postoperative measurements for the Lysholm- and Tegner scores, IKDC-patient subjective assessment, KT-1000 measurements, pivot shift test, IKDC score and one-leg hop test. A pivot shift phenomenon (glide) was still present in 43 (50%) patients and correlated with lower levels of activity ($P < 0.022$).

At 10-year follow-up, radiological signs of osteoarthritis were present in 53.5% of the subjects. The rate of osteoarthritis after meniscectomy and ACL reconstruction was 64.5% in comparison with 20% in the group with isolated ACL reconstruction. Predictors for osteoarthritis were patient age ≥ 30 years at the time of ACL reconstruction, cartilage status ≥ ICRS (International Cartilage Research Society) grade 2 at the time of ACL reconstruction, history of medial meniscectomy and preoperative one-leg hop test C and D. Multivariate logistic regression analysis showed the status of the medial meniscus and ICRS grade 3 cartilage condition at the time of ACL reconstruction to be significant predictors for knee osteoarthritis. A history of medial meniscectomy before or at the time of ACL reconstruction increased the risk of knee osteoarthritis 4 times (95 % CI 1.41–11.5). An ICRS grade 3 at the time of ACL reconstruction increased the risk of knee osteoarthritis 5.2 times (95 % CI 1.09–24.8). Activity level (Tegner score ≥ 6) and a positive pivot shift test were not correlated with osteoarthritis.

In conclusion, transtibial ACL reconstruction with 4-strand hamstring autograft and accelerated brace-free rehabilitation restored anteroposterior knee stability. Clinical parameters and patient satisfaction improved significantly. There is no evidence in our study that ACL reconstruction prevents long-term knee osteoarthritis.

The general discussion in **Chapter 8** focuses on the current perspective on accelerated rehabilitation after ACL reconstruction. A new model for ACL graft remodelling research finalizes the chapter.

It is agreed that ACL graft healing can only progress if mechanical loading occurs: however, the most adequate magnitude at varying phases of healing is still not clarified. Accelerated rehabilitation needs to be as aggressive as possible in restoring function while still maintaining an optimal tissue-healing environment.

The goals of pre- and postoperative rehabilitation, as defined in the standardized accelerated brace-free rehabilitation protocol of this thesis (Appendix 1), cohere with current scientific insights in ACL rehabilitation after hamstring tendon ACL reconstruction. Recommendations for further improvements are: (1) restoring preoperative hyperextension if present; (2) closed kinetic chain (CKC) quadriceps exercises are preferred in the first 12 weeks of rehabilitation. Start CKC exercises in 50°-90° of knee flexion, gradually building range of motion to 0°-90° and resistance as tolerated. Inducing bilateral fatigue improves loading symmetry in CKC exercises; (3) a combination of CKC and open kinetic chain (OKC) quadriceps exercises is recommended. It is safest to start OKC quadriceps exercises at 12 weeks in 0°-90°, adding progressive concentric and eccentric exercises at 13 weeks. Eccentric training is recommended for quadriceps strengthening exercises with focus of training both legs; (4) synovitis of the knee should guide the rehabilitation pace and; (5) focus on quality of movement, such as dynamic knee valgus is important in ACL rehabilitation.

This thesis has shown that despite the large number of publications, no conclusive guidelines currently exist to determine when a safe return to unrestricted activity is permitted. The development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual return to sports is greatly needed and offers opportunities for further research. Identifying specific patient phenotypes, possibly gender-related, may allow a more customized rehabilitation approach. Studies identifying sport-specific differences in ACL reconstruction outcomes in athletes could further enhance different time frames of rehabilitation after ACL reconstruction.

The striking similarities between tendinopathy models and ACL hamstring tendon graft remodelling inspired me to contemplate new horizons in ACL remodelling and rehabilitation research. In view of tendon adaptation to load and the ceiling effect in collagen synthesis by fibroblasts, it would be interesting to study the development of preoperative strategies to increase the collagen content in hamstring tendons prior to their use as ACL tendon grafts. This could increase ACL tendon graft strength and possibly decrease the rerupture rates of ACL grafts in sports-related activities.

Women show less increase in collagen synthesis, need longer for tendon adaptation to loading and are more susceptible to soft tissue (re)injuries than men. This estrogen-related collagen synthesis may necessitate different rehabilitation strategies for men and women for optimal ACL graft healing. Future gender-based research might lead to better outcome after ACL reconstruction.

Genetic predisposition seems related to the development of tendinopathy. Genetic variants modify the susceptibility of tendons to matrix disturbance and weaken tendon strength. Interestingly, the genes encoding these proteins have also been associated with ACL rupture. This offers another opportunity for research to investigate if genetically-prone tendinopathy patients suffer more reruptures after autograft tendon ACL reconstruction. If so, these patients might benefit from allograft tissue instead of autograft tendons as ACL graft.

This thesis has shown that biopsy studies of the peripheral structures of the hamstring tendon ACL autograft show typical phases of remodelling similar to the pathogenesis models of tendinopathy. As the centre of the graft seems to be less involved in healing and strength in tendinopathy, prevention of neovascularization and pathological nerve ingrowth into the ACL tendon graft is a new area for research. This might offer new horizons for optimal treatment and outcome after ACL reconstruction. Imaging techniques for tendinopathy may monitor treatment and biological effects in the remodelling phases of ACL grafts by time- and dose-specific loading of different rehabilitation modalities.

In summary, future research will have to be directed to: (1) optimizing ACL reconstructions to fully restore the anatomy and function while providing the mechanical strength of the intact ACL; (2) developing biological treatment options that impact on graft healing especially during the early and proliferation phase to optimize extracellular matrix remodelling and avoid excessive remodelling activity that might impair mechanical integrity of the healing graft and; (3) to better differentiate the 'good' from the 'bad' remodelling changes, so that the time to return to sports without any restrictions can be reduced.

NEDERLANDSE SAMENVATTING

Een letsel van de voorste kruisband (VKB) kan leiden tot een instabiel gevoel van de knie met een verhoogd risico op schade aan menisci, kraakbeen en collateraalbanden. Een reconstructie van de VKB is geïndiceerd bij een functionele instabiliteit van de knie en is de 6e meest uitgevoerde orthopedische operatie.

De meest recente incidentiecijfers van VKB reconstructies in Nederland worden geschat op 46 per 100.000 personen per jaar. De incidentie van VKB reconstructies neemt toe, met name bij vrouwen, patiënten jonger dan 20 jaar en ouder dan 40 jaar.

De populariteit van autologe hamstringpezen als transplantaat voor VKB reconstructies stijgt en het succespercentage varieert tussen 55-95%. Een succesvolle VKB reconstructie vereist kennis van de anatomische plaatsing van de VKB graft, mechanische eigenschappen van het geselecteerde transplantaat, fixatiematerialen en de biologische processen van de genezende graft. Deze factoren beïnvloeden rechtstreeks de biomechanische eigenschappen van het kniegewricht met gevolgen voor de revalidatie en het moment waarop de knie weer normaal kan functioneren.

Doelstelling van dit proefschrift is het verkrijgen van nieuwe inzichten in de karakteristieken en biologische kenmerken van hamstringpezen alsmede de lange termijnresultaten na VKB reconstructies met hamstringpezen in combinatie met een versnelde revalidatie zonder kniebrace (zo geheten 'accelerated brace-free rehabilitation'). In alle klinische studies van dit proefschrift is een identieke operatietechniek toegepast met een gestandaardiseerd 'accelerated brace-free rehabilitation' protocol.

Hoofdstuk 1 geeft een historisch overzicht van VKB reconstructies met hamstringpezen en 'accelerated brace-free rehabilitation.' Hamstringpees VKB reconstructies hebben inmiddels een 25 jarige staat van dienst. De ontwikkeling van nieuwe arthroscopische richtapparatuur en fixatiemethoden in de jaren 90 bood de mogelijkheid om de VKB reconstructie te verrichten met intra-articulair boren van de femurtunnel. Het laatste decennium van de vorige eeuw was ook de transitieperiode van patellapees naar hamstringpezen als autograft voor VKB reconstructies in Nederland. Voorstanders beschreven dat hamstringpezen sterker zijn, een grotere dwarsdoorsnede hebben voor 'footprint' herstel met betere tunnelpasvorm, betere biologische ingroei en stabiliteit, minder 'donor site' morbiditeit en minder klachten van het strekapparaat in vergelijking met patellapees grafts. Terugkeer naar sportniveau was toegestaan na 4-6 maanden. Deze chirurgische VKB reconstructie met versnelde revalidatie zonder kniebrace werd al snel populair en wordt tot op heden veelvuldig toegepast.
De juiste balans tussen spierkrachttraining en belasting van de VKB graft blijkt een grote uitdaging in de postoperatieve revalidatie na een VKB reconstructie. In dit eerste hoofdstuk worden het onderzoeksperspectief en de doelstelling van het proefschrift gepresenteerd.

In **Hoofdstuk 2** wordt een overzicht gegeven van de huidige kennis over 'accelerated brace-free rehabilitation' na hamstringpees VKB reconstructies. Een systematische review is verricht volgens PRISMA richtlijnen (Preferred Reporting Items for Systematic Reviews and Meta-Analysis), van 1 januari 1990 tot 31 december 2014. De primaire doelstelling van de studie was het beoordelen van de klinische uitkomst na VKB reconstructies met 'accelerated brace-free rehabilitation' bij volwassenen. De secundaire doelstelling was de analyse van het effect van versnelde revalidatie op bottunnelwijdte, regeneratie van hamstringpezen en 'return to sports' na VKB reconstructie.

De resultaten van deze studie lieten zien dat na een hamstringpees VKB reconstructie met 'accelerated brace-free rehabilitation': (1) anatomische VKB reconstructies beter zijn dan niet-anatomische reconstructies; (2) er geen verschil is tussen 'single'- en 'double' bundel reconstructies; (3) geslacht en leeftijd niet geassocieerd zijn met klinische uitkomst; (4) verwijding van zowel femorale als tibiale tunnels plaats vindt; (5) vroege start van open ketenoefeningen na 4 weken in een beperkt bewegingstraject van de knie (90°-45°) evenals progressieve concentrische en excentrische oefeningen na 12 weken de uitkomst niet veranderen; (6) Nintendo Wii® activiteiten fysiotherapie doelstellingen kunnen helpen bereiken; (7) hamstringpezen regenereren na verwijdering en (8) biologische kennis 'return to sports' na 4-6 maanden niet ondersteunt.

Concluderend kan 'accelerated brace-free rehabilitation' bijdragen aan een succesvolle hamstringpees VKB reconstructie bij volwassenen van alle leeftijden en geslacht. Verder wetenschappelijk onderzoek is nodig ter definiëring van de optimale balans tussen belasting en genezing van de graft in de verschillende fasen van revalidatie na een VKB reconstructie. Valide criteria moeten worden vastgesteld voor een revalidatie op maat evenals een veilige terugkeer naar sport-specifieke training en 'return to play'.

In **Hoofdstuk 3 tot en met 6** heb ik ervoor gekozen de kennis te verdiepen over hamstringpezen die worden gebruikt voor VKB reconstructies. Deze hoofdstukken vormen het centrale deel van het proefschrift met als focus de maat van hamstringpees transplantaten, regeneratie van hamstringpezen, en biologie en remodellering van humane hamstringpees autografts.

Een preoperatieve voorspelbaarheid van de maat van een hamstringpees autograft zou de planning van knieligamentchirurgie faciliteren en de noodzaak tot gebruik van allografts kunnen verminderen bij complexe kniebandreconstructies. Dit zou tot een kostenbesparing en een betere kwaliteit van de ligamentreconstructies met betrekking tot kans op reruptuur van de graft en postoperatieve kniestabiliteit kunnen leiden.

Doelstelling van **Hoofdstuk 3** is het beoordelen van de preoperatieve voorspelbaarheid van zowel lengte als diameter van hamstringpees autografts aan de hand van antropometrische parameters en patiëntkenmerken. In deze observationele studie zijn 725 opeenvolgende patiënten geïncludeerd die gepland stonden voor een VKB reconstructie. Geslacht, leeftijd, lengte en gewicht van de patiënten zijn preoperatief gedocumenteerd. De lengte van de semitendinosus- en gracilispezen zijn gemeten na verwijdering tijdens de VKB reconstructie. De diameter van de geprepareerde hamstring autograft werd geregistreerd. De correlatie tussen de lengte en diameter van de hamstringpezen en de antropometrische parameters werd berekend aan de hand van lineaire en logistische regressie analyse.

De resultaten lieten zien dat de gemiddelde lengte van de semitendinosuspees en gracilispees respectievelijk 28.9 ± 3.1 en 27.7 ± 3.0 cm was. De lengte van de semitendinosuspees was < 21 cm bij 2 patiënten (0.3%). De lengte van de gracilispees bleek < 21 cm bij 12 patiënten (1.7 %). De graftdiameter was ≤ 7 mm bij 42 patiënten (5.8%), 8 mm bij 359 patiënten (49.7%) en ≥ 9 mm bij 322 patiënten (44.5%). Er bestond een correlatie tussen het geslacht en graft diameter < 8 mm. Een op de negen vrouwen had een graftdiameter < 8 mm, bij mannen was deze ratio 1:36.

Concluderend kunnen lengte en diameter van autograft hamstringpezen preoperatief worden voorspeld aan de hand van de lengte en gewicht van de patiënt. De lengte van de semitendinosuspees en gracilispees is onafhankelijk gerelateerd aan patiëntlengte. Een dunnere graft diameter is gecorreleerd met het vrouwelijk geslacht.

Hoofdstuk 4 beschrijft de aangroei van hamstringpezen in het bovenbeen nadat deze zijn verwijderd als VKB transplantaat. Onze hypothese is dat zowel regeneratie van de semitendinouspees als de gracilispees plaatsvindt na te zijn geoogst voor een VKB reconstructie en dat de isokinetische spierkracht beter herstelt indien de peesregeneratie distaal van de gewrichtsspleet van de knie plaatsvindt.

Een prospectieve MRI scan analyse van beide benen vond plaats bij 22 patiënten die gepland stonden voor een VKB reconstructie. De studie bestond uit 2 delen.
Het eerste gedeelte betrof een prospectieve MRI studie ter beoordeling van de regeneratie van de semitendinosuspees en gracilispees na VKB reconstructie met hamstringpezen. Consecutieve patiënten die voldeden aan de inclusiecriteria van het studieprotocol ondergingen een MRI scan van beide benen preoperatief en 2 weken, 6 weken en 12 maanden postoperatief. De MRI parameters waren peesregeneratie en peesmorfologie, spierretractie en spierdwarsdoorsnede.
Het tweede gedeelte van de studie was een prospectief, dubbelblinde analyse van isokinetische spierkracht van de quadriceps- en hamstringspieren van beide benen. De patiënten werden preoperatief beoordeeld evenals 6 en 12 maanden postoperatief. Aanvullend werden de Tegner-, Lysholm- en International Knee Documentation Committee (IKDC) scores afgenomen. Tevens werd de bovenbeensomvang en de KT-1000 test bij 89 and 133 Newton (MEDmetric Co., San Diego, CA, USA) vergeleken van beide benen.

De studie heeft aangetoond dat de gracilispees bij alle patiënten weer aangroeide. De regeneratie van de semitendinosuspees vond plaats bij 14 patiënten. Na 1 jaar was de oppervlakte van de M. semitendinosus en M. gracilis verminderd vergeleken met preoperatief ($P < 0.01$) alsmede het contralaterale been ($P < 0.01$). De dwarsdoorsnede van de M. semitendinosus nam af als de semitendinosuspees niet aangroeide ($P = 0.05$). De dwarsdoorsnede van de M. gracilis nam toe bij regeneratie van de gracilispees distaal van de gewrichtspleet ($P = 0.01$). De retractie van de M. semitendinosus was groter bij afwezige regeneratie van de semitendinosuspees ($P = 0.02$).

De conclusie van de studie is dat hamstringpezen regenereren nadat ze zijn verwijderd als graft voor een VKB reconstructie. Er is geen correlatie tussen peesregeneratie en isokinetische hamstringspierkracht.

De in vivo humane VKB graft biopsiestudie in **Hoofdstuk 5** illustreert de histologie en morfologie van hamstringpees autograft remodellering in diverse fasen na succesvolle VKB reconstructie met een gestandaardiseerd 'accelerated brace-free rehabilitation' protocol. Het betrof een gezamenlijk onderzoeksproject tussen het Máxima Medisch Centrum (Eindhoven-Veldhoven) en het Charité Centre for Musculoskeletal Surgery (Berlijn, Duitsland). De hypothese van de studie was dat de hamstringpees VKB autograft een remodelleringsproces ondergaat waarbij het histologisch beeld vergelijkbaar wordt met de morfologie van een originele VKB en dat dit proces 1 jaar na VKB reconstructie is afgerond.

Bij 67 patiënten werd een biopt afgenomen van het middelste gedeelte van de VKB autograft na klinisch succesvol hamstringpees VKB reconstructie. De biopten werden ingedeeld in 3 groepen afhankelijk van de tijdsinterval tussen de biopsie en de VKB reconstructie: groep 1 (6–12 maanden; n = 15), groep 2 (13–24 maanden; n = 16) en groep 3 (> 24 maanden; n = 11). Biopten van oorspronkelijke hamstringpezen (n = 17) en VKB (n = 8) dienden als controlegroep. Cellulaire-, vasculaire- en myofibroblast dichtheid evenals collageen alignement werden geanalyseerd middels haematoxylin–eosin, Masson-Goldner-Trichrom en immunohistochemische kleuringsprotocollen.

De studie liet zien dat het totaal aantal cellen toegenomen was, in vergelijking met oorspronkelijke hamstringpezen (330.4/mm^2) in groep 1-3 (groep 1 = 482.0/mm^2 ($P = 0.036$); groep 2 = 850.9/mm^2 ($P = 0.005$); en groep 3 = 595.6/mm^2 ($P = 0.043$)). De vasculaire dichtheid was niet significant verschillend tussen de groepen. De myofibroblast dichtheid was hoger in groep 2 (199.6/mm^2) vergeleken met oorspronkelijke hamstringpezen (1.9/mm^2, $P = 0.014$). De aanwezigheid van myofibroblasten is kenmerkend voor een actief remodelleringsproces bij VKB grafts. De toegenomen myofibroblast dichtheid tussen 13 en 24 maanden na de VKB reconstructie liet zien dat de remodellering van VKB grafts bij mensen langer duurt dan is aangetoond in dierstudies. De collageenoriëntatie was onregelmatig tot 12 maanden na VKB operatie. Daarna werd de collageenoriëntatie regelmatiger, met een aanpassing maar geen volledig herstel van de morfologie van de oorspronkelijke VKB. Gedurende de eerste 12 maanden waren cellen vooral ovoïd van vorm. De celmorfologie veranderde naar spoelvormig in groep 2 en naar voornamelijk smalle langwerpige cellen na 2 jaar.

Concluderend ondergaan hamstringpees VKB autografts kenmerkende fasen van remodellering. Dit proces is nog niet afgerond 2 jaar na VKB reconstructie. Het remodelleringsproces van VKB grafts duurt bij mensen langer dan bij dieren.

In **Hoofdstuk 6** wordt een overzicht gepresenteerd van de huidige kennis over remodellering van hamstringpees VKB transplantaten. Mens- en dierstudies worden vergeleken en de consequenties voor de revalidatie besproken. Een systematische review van de bestaande literatuur is verricht tussen 1982 en 2012, met nadruk op in vivo studies over intra-articulaire VKB graft remodellering.

Dier- en humaan in vitro en in vivo onderzoek heeft aangetoond dat er 3 karakteristieke fasen van de VKB graft genezing bestaan: een 'early graft healing phase' met centrale graft necrose, hypocellulariteit en afwezige neovascularisatie van het graft weefsel, gevolgd door een 'phase of proliferation', de periode van meest intensieve remodellering en neovascularisatie en tenslotte een 'ligamentization phase' met karakteristieke herstructurering van de graft naar de eigenschappen van de originele VKB. Een volledig herstel van de biologische en biomechanische eigenschappen van de oorspronkelijke VKB wordt echter nooit bereikt.
Het is belangrijk te weten dat de remodellering van VKB grafts bij mensen langer duurt dan bij dieren omdat huidige revalidatieprotocollen na VKB reconstructies zijn geëxtrapoleerd uit data van dierstudies. Deze nieuwe inzichten in de vertraagde VKB graft remodellering bij in vivo humane studies kunnen leiden tot nieuwe postoperatieve revalidatieprotocollen na hamstringpees VKB reconstructies.

De klinische en radiologische lange termijn resultaten na hamstringpees VKB reconstructies met 'accelerated brace-free rehabilitation' worden gepresenteerd in **Hoofdstuk 7**. Het betreft een prospectieve studie bij 100 patiënten met analyse preoperatief en 10 jaar postoperatief. De klinische uitkomst is gemeten aan de hand van de Lysholm-, Tegner- en IKDC scores, KT-1000 test en beenomvang. De radiologische evaluatie vond plaats middels de volgende röntgenopnamen van de knie: AP belast, lateraal, Rosenberg en axiale patella. De Ahlbäck en Kellgren&Lawrence classificatie zijn gebruikt ter beoordeling van de mate van knie-artrose. Univariate and multivariate logistische regressies maakten deel uit van de statistische analyse.

De resultaten lieten een significante verbetering (P < 0.001) zien tussen de preoperatieve en postoperatieve Lysholm- en Tegner scores, IKDC-'patient subjective assessment', KT-1000 test, pivot shift test, IKDC score en de 'one-leg hop' test. Een pivot shift fenomeen (glide) was aanwezig bij 43 (50%) patiënten en was gecorreleerd met een lager activiteitenniveau (P < 0.022).

Na 10 jaar follow-up had 53.5% van de patiënten radiologische tekenen van gonartrose. De mate van artrose na VKB reconstructie met bijkomende mediale meniscectomie was 64.5% vergeleken met 20% bij patiënten met een geïsoleerde VKB reconstructie. Voorspellers voor artrose waren leeftijd ≥ 30 jaar ten tijde van de VKB reconstructie, kraakbeenconditie ≥ ICRS (International Cartilage Research Society) graad 2 ten tijde van de VKB operatie, mediale meniscectomie, en een preoperatieve 'one-leg hop' test graad C en D. De multivariate logistische regressie heeft aangetoond dat de status van de mediale meniscus en de ICRS graad 3 kraakbeenconditie ten tijde van de VKB reconstructie significante voorspellers zijn voor knie-artrose. Een voorgeschiedenis van mediale meniscectomie voor of ten tijde van de VKB reconstructie leidde tot een 4x hoger risico op artrose (95 % CI 1.41–11.5). Een ICRS graad 3 kraakbeenconditie ten tijde van de VKB reconstructie veroorzaakte een 5.2x hoger risico op gonartrose (95 % CI 1.09–24.8). Er was geen correlatie tussen artrose en het activiteitenniveau (Tegner score ≥ 6) of een positieve pivot shift test.

Concluderend wordt de voorachterwaartse kniestabiliteit hersteld na een transtibiale hamstringpees VKB reconstructie en 'accelerated brace-free rehabilitation'. Patiënttevredenheid en de klinische parameters verbeteren significant. Er is geen bewijs in onze studie dat een VKB reconstructie beschermt tegen gonartrose op de lange termijn.

De discussie in **Hoofdstuk 8** bestaat uit 2 delen. Het eerste deel bespreekt de huidige inzichten in 'accelerated brace-free rehabilitation' na VKB reconstructie. Aanbevelingen voor verbetering van het revalidatieprotocol worden gedaan. Het tweede deel presenteert een nieuw onderzoekmodel voor VKB graft remodellering.

De genezing van het VKB transplantaat kan alleen plaats vinden bij mechanische belasting; echter, de juiste mate van belasting in de verschillende fasen van graft remodellering is nog onbekend. De doelen van pre- en postoperatieve revalidatie, zoals gedefinieerd in het gestandaardiseerd 'accelerated brace-free rehabilitation' protocol van dit proefschrift (Appendix 1) zijn coherent met de huidige inzichten in VKB revalidatie na hamstringpees VKB reconstructie. Aanbevelingen voor verbetering zijn: (1) herstel van preoperatieve hyperextensie indien aanwezig; (2) gesloten keten quadriceps oefeningen genieten de voorkeur in de eerste 12 weken van de revalidatie. Start deze oefeningen in 50°-90° knieflexie, geleidelijk opbouwend naar 0°-90° met weerstand die de patiënt kan verdragen. Het opwekken van bilaterale vermoeidheid verbetert de symmetrie van belasting in gesloten ketenoefeningen; (3) een combinatie van gesloten en open ketenoefeningen wordt aanbevolen. Het is het veiligst om de open ketenoefeningen te beginnen 12 weken na de VKB reconstructie in 0°-90° knieflexie, aangevuld met progressieve concentrische en excentrische oefeningen na 13 weken. Excentrisch trainen wordt aanbevolen voor quadriceps spierkracht van beide benen; (4) synovitis van de knie stuurt het revalidatietempo; en (5) focus op kwaliteit van bewegen, zoals het dynamisch knie valgus moment, is belangrijk tijdens de VKB revalidatie.

Dit proefschrift heeft aangetoond dat, ondanks de veelvuldige publicaties over het onderwerp, er nog geen richtlijnen bestaan ter bepaling van het moment van veilige terugkeer naar onbeperkte activiteiten. Studies naar valide criteria hiervoor zijn noodzakelijk en bieden mogelijkheden voor verder onderzoek. Het identificeren van patiënt-specifieke fenotypes evenals sport-specifieke verschillen bij sporters kunnen bijdragen aan een betere revalidatie op maat na een VKB reconstructie.

Het tweede deel van dit hoofdstuk presenteert nieuwe ideeën voor onderzoek naar de genezing van VKB transplantaten. Nieuwe in vivo biopsiestudies naar VKB graft remodelling zijn medisch ethisch moeilijk te verantwoorden bij mensen. De opvallende overeenkomsten tussen de genezing van pezen bij tendinopathie en VKB graftgenezing hebben me geïnspireerd om na te denken over een nieuw onderzoekmodel voor VKB remodellering en revalidatie.

Tendinopathie onderzoek heeft aangetoond dat pezen structureel kunnen aanpassen aan belasting, echter met een plafondeffect in collageensynthese door fibroblasten. Het is interessant om preoperatieve strategieën te bedenken om de collageenconcentratie van hamstringpezen te verhogen voordat ze gebruikt worden als VKB transplantaat. Dit zou kunnen leiden tot een sterkere VKB graft met minder kans op een VKB reruptuur bij sport-gerelateerde activiteiten.

Vrouwen hebben een verminderde toename in collageensynthese, langere tijdsduur voor peesaanpassing aan belasting, en meer kans op weke delenletsels in vergelijking met mannen. Deze oestrogeen-gebonden collageensynthese zou een reden kunnen zijn om verschillende revalidatieprotocollen te ontwikkelen voor vrouwen versus mannen ten behoeve van een optimale VKB graft genezing. Toekomstig geslachtsgebonden onderzoek zou tot betere uitkomsten na VKB reconstructies kunnen leiden.

Er is een relatie tussen genetische predispositie en de ontwikkeling van tendinopathie. Genetische variaties beïnvloeden matrixstoornissen van pezen en verzwakken de peessterkte. Het is interessant te weten dat de genen die deze eiwitten coderen ook zijn geassocieerd met de kans op een VKB ruptuur. Dit biedt de mogelijkheid om te onderzoeken of patiënten met een genetisch toegenomen risico op tendinopathie ook vaker VKB rerupturen hebben. Wellicht dat deze groep patiënten meer profijt heeft van een allograft in plaats van een autograft VKB reconstructie.

De biopsiestudie in dit proefschrift heeft aangetoond dat de perifere structuren van het hamstringpees VKB transplantaat typische fasen van remodellering ondergaan die vergelijkbaar zijn met de pathogenese modellen bij tendinopathie. Het centrale gedeelte van de graft lijkt minder betrokken bij de genezing en mechanische sterkte van de pees. Naar analogie van de tendinopathie pathogenese kan neovascularisatie en pathologische zenuwingroei de sterkte van de VKB graft verzwakken met meer kans op reruptuur bij te grote belasting tijdens de revalidatie. Preventie van neovascularisatie en zenuwingroei in het VKB transplantaat biedt nieuwe mogelijkheden voor onderzoek naar een optimale behandeling en betere uitkomst na VKB reconstructies. Medische beeldtechnieken die gebruikt worden bij tendinopathie kunnen behulpzaam zijn als monitor van de biologische effecten tijdens de remodelleringsfasen van de VKB graft bij dosis- en tijd-specifieke belasting van verschillende revalidatieprotocollen.

Samenvattend moet toekomstig onderzoek zijn gericht op: (1) optimalisering van anatomie en functie van VKB reconstructies om de volledige mechanische sterkte van de originele VKB te herstellen; (2) ontwikkeling van biologische behandelingen die vooral in de vroege fasen van genezing van de VKB graft gunstige invloed hebben op de extracellulaire matrix remodellering zonder dat excessieve remodellering plaats vindt die de mechanische integriteit van het transplantaat kan verzwakken en; (3) betere differentiatie tussen 'goede' en 'slechte' remodelleringsprocessen, zodat de tijdsduur tot terugkeer naar sport zonder beperkingen kan worden verminderd.

RÉSUMÉ EN FRANÇAIS

Les patients victimes d'une rupture du ligament croisé antérieur (LCA) peuvent avoir un sentiment d'instabilité du genou et sont à risque de blessures concomitantes des ménisques, du cartilage et des ligaments collatéraux. L'instabilité fonctionnelle du genou peut être traitée par une reconstruction du LCA, qui est classée en 6e position des opérations orthopédiques les plus pratiquées.

L'incidence la plus récente de reconstructions du LCA aux Pays-Bas a été estimée à 46 par 100.000 personnes par an. L'incidence des reconstructions du LCA augmente, en particulier chez les femmes, ainsi que chez les patients de moins de 20 ans et ceux de plus de 40 ans.

Les tendons ischio-jambiers continuent de gagner en popularité en tant que greffe autologue pour la reconstruction du LCA et le taux de réussite varie entre 55 et 95%. Une reconstruction du LCA réussie nécessite la compréhension de plusieurs facteurs: le placement anatomique de la greffe, les propriétés mécaniques du tissu greffé choisi, le comportement mécanique et la force de fixation des matériaux de fixation, ainsi que les processus biologiques qui se produisent au cours de la cicatrisation de la greffe. Ces facteurs affectent directement les propriétés mécaniques de l'articulation du genou après une reconstruction du LCA et, par conséquent, déterminent la durée de rééducation nécessaire pour que l'articulation du genou puisse à nouveau fonctionner normalement.
L'objectif de cette thèse était d'acquérir des connaissances sur les caractéristiques et la biologie des tendons ischio-jambiers, ainsi que les résultats cliniques à long terme après reconstruction du LCA par autogreffe aux ischio-jambiers avec rééducation accélérée sans attelle. La même technique chirurgicale et le même protocole normalisé de rééducation accélérée ont été utilisés dans toutes les études cliniques de cette thèse.

Le **Chapitre 1** présente une perspective historique de la reconstruction du LCA par autogreffe aux tendons ischio-jambiers et de la rééducation accélérée sans attelle. Les reconstructions du LCA par autogreffe aux ischio-jambiers ont une expérience de 25 ans. Dans les années 1990, les progrès dans les guides arthroscopiques et de meilleures techniques de fixation de greffe ont permis la reconstruction du LCA par incision unique avec forage intra-articulaire du tunnel fémoral. Aux Pays-Bas, les années 1990 ont été la décennie de transition de l'autogreffe au tendon rotulien à l'autogreffe aux tendons ischio-jambiers. Les promoteurs ont soutenu que les tendons ischio-jambiers étaient le choix de greffe préféré pour la reconstruction du LCA en raison d'une plus grande force, d'une plus grande surface de section transversale pour la recréation de l'empreinte, de la conformité du tunnel à la greffe, de l'incorporation biologique, de la stabilité et d'une morbidité moindre du site donneur et de moins de douleur antérieure du genou par rapport aux autogreffes os-tendon rotulien-os. Le retour aux sports était autorisé à 4-6 mois après la reconstruction du LCA. En conséquence, cette technique de reconstruction chirurgicale est devenue populaire en combinaison avec le protocole de rééducation accélérée sans attelle et elle est encore largement pratiquée aujourd'hui.

Un défi majeur dans la rééducation postopératoire après reconstruction du LCA est l'optimisation de l'équilibre entre les exercices de renforcement musculaire et la charge de la greffe, sans compromettre l'intégrité de la greffe. Le point de vue de la recherche sur le sujet est lié à l'objectif de la thèse dans ce premier chapitre.

Le **Chapitre 2** présente un aperçu des connaissances actuelles sur la rééducation accélérée sans attelle après reconstruction du LCA par autogreffe aux tendons ischio-jambiers.
Une revue systématique a été réalisée selon les lignes directrices de PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis - éléments de rapport préférés pour les examens systématiques et la méta-analyse) du 1er janvier 1990 au 31 décembre 2014. L'objectif principal de cette revue systématique était d'étudier la rééducation accélérée sans attelle après reconstruction du LCA chez les adultes. Les objectifs secondaires étaient l'influence de la rééducation accélérée sur la dilatation du tunnel, la régénération du tendon et le temps de retour au sport après une reconstruction du LCA.

Les résultats de cette étude ont montré qu'après une reconstruction du LCA par autogreffe aux ischio-jambiers avec rééducation accélérée sans attelle: (1) les reconstructions anatomiques montrent de meilleurs résultats que les reconstructions non-anatomiques; (2) il n'y avait pas de différence entre les reconstructions à simple et double faisceaux; (3) le sexe et l'âge n'ont pas eu d'effet sur les résultats cliniques; (4) une dilatation des tunnels fémoral et tibial s'est produite; (5) le démarrage précoce des exercices en chaîne cinétique ouverte à 4 semaines dans une amplitude de mouvement limitée (90°-45°) et des exercices concentriques et excentriques progressifs à partir de 12 semaines n'ont pas modifié les résultats; (6) les activités de Nintendo Wii® peuvent aider à atteindre les objectifs de physiothérapie; (7) les tendons ischio-jambiers se régénèrent après le prélèvement et (8) les connaissances biologiques n'ont pas appuyé le retour au sport à 4-6 mois.

En conclusion, la rééducation accélérée sans attelle peut contribuer au succès de la reconstruction du LCA par autogreffe aux tendons ischio-jambiers chez les patients adultes de tous âges et sexes. Des recherches complémentaires sont nécessaires pour définir l'équilibre optimal de charge de la greffe et de cicatrisation de la greffe dans les différentes phases de rééducation après une reconstruction du LCA, ainsi que l'élaboration d'évaluations valides, fondées sur des critères visant à déterminer des phases personnalisées de rééducation et de préparation à un entraînement spécifique pour le retour au sport.

Dans les **Chapitres 3 à 6**, j'ai choisi d'approfondir les connaissances sur les autogreffes de tendons ischio-jambiers utilisées pour la reconstruction du LCA. Ces chapitres couvrent la partie centrale de la thèse et se concentrent sur la taille de la greffe, la régénération, la biologie et le remodelage des autogreffes de tendons ischio-jambiers humains.

La prévision de la taille de greffe des tendons ischio-jambiers pourrait faciliter la planification préopératoire de la chirurgie du ligament du genou et pourrait réduire la nécessité d'allogreffes pour les reconstructions ligamentaires complexes du genou. Cela réduirait les coûts chirurgicaux et augmenterait la qualité des reconstructions du ligament en ce qui concerne le risque de rupture de la greffe et la stabilité postopératoire.

L'objectif du **Chapitre 3** était d'analyser la prévisibilité préopératoire de la longueur et du diamètre des autogreffes aux tendons ischio-jambiers à l'aide des paramètres anthropométriques et des caractéristiques des patients. Dans cette étude observationnelle, 725 patients caucasiens consécutifs, en attente d'une reconstruction du LCA, ont été inclus. Le sexe, l'âge, la taille et le poids du patient avaient été enregistrés en préopératoire. Après enlèvement, les longueurs des deux tendons semi-tendineux et gracile ont été mesurées. Le diamètre de l'autogreffe de LCA finale de 4 brins a été enregistré. La corrélation entre la longueur et le diamètre des greffes tendineuses et des différents paramètres anthropométriques a été évaluée par des analyses linéaires et de régression logistique.

Les résultats ont montré que les longueurs moyennes des autogreffes de tendons semi-tendineux et gracile étaient respectivement de 28,9 ± 3,1 cm et 27,7 ± 3,0 cm. Deux patients (0,3%) avaient une longueur de tendon semi-tendineux inférieure à 21 cm. Douze patients (1,7%) avaient des tendons graciles mesurant moins de 21 cm. Un total de 42 patients (5,8%) avaient une greffe de diamètre ≤ 7 mm, 359 patients (49,7%) avaient une greffe de diamètre de 8 mm, et 322 patients (44,5%) des diamètres ≥ 9 mm. Une corrélation a été trouvée entre le sexe et le diamètre de greffe < 8 mm. Une patiente sur neuf avait un diamètre < 8 mm, le ratio chez les hommes était de 1 sur 36.

En conclusion, la longueur et la taille de l'autogreffe aux ischio-jambiers peuvent être prédites chez les Caucasiens. La longueur des tendons semi-tendineux et gracile était indépendamment liée à la taille du patient. Un diamètre de greffe plus petit était lié au sexe féminin.

Le **Chapitre 4** décrit la régénération des tendons ischio-jambiers après le prélèvement pour la reconstruction du LCA. Notre hypothèse était que les tendons semi-tendineux et gracile régénèrent après le prélèvement pour la reconstruction du LCA et que la force musculaire isocinétique est mieux restaurée en cas de régénération des tendons ischio-jambiers distale de la ligne d'articulation du genou.

Vingt-deux patients programmés pour une reconstruction du LCA ont subi une analyse IRM prospective des deux jambes. L'étude consistait en 2 parties.
La première partie était une étude IRM prospective pour déterminer la régénération des tendons semi-tendineux et gracile après reconstruction du LCA. Des patients consécutifs, qui remplissaient les critères d'entrée, tels que définis par le protocole de l'étude, ont subi une IRM préopératoire des deux jambes, ainsi qu'une IRM postopératoire 2 semaines, 6 mois et 12 mois après l'opération. Les paramètres IRM étaient la régénération et la morphologie des tendons, la rétraction du muscle et la surface de section transversale du muscle.
La deuxième partie est une étude prospective, en double-aveugle de la force isocinétique du quadriceps et des muscles ischio-jambiers des deux jambes. Les patients ont été examinés avant l'intervention et 6 et 12 mois après l'opération. Les patients ont été évalués à l'aide des scores de Tegner, de Lysholm et du Comité international de documentation du genou (IKDC – International Knee Documentation Committee). Les mesures de circonférence de la partie supérieure de la jambe et des tests de laxisme des deux jambes ont été effectués au KT-1000 à 89 et 133 Newton (MEDmetric Co., San Diego, CA, USA).

L'étude a montré que la régénération du tendon gracile après reconstruction du LCA a eu lieu chez tous les patients. La régénération du tendon semi-tendineux est survenue chez 14 patients. A 1 an, la zone de surface des muscles semi-tendineux et gracile a diminué par rapport au préopératoire ($P < 0,01$) et à la jambe controlatérale ($P < 0,01$). La surface de section transversale du muscle semi-tendineux a diminué en l'absence de régénération du tendon ($P = 0,05$). La surface de section transversale du muscle gracile était plus grande dans le cas de régénération distale de la ligne d'articulation ($P = 0,01$). La rétraction musculaire du muscle semi-tendineux avait augmenté en cas de non-régénération ($P = 0,02$).

Nous en avons conclu que les tendons ischio-jambiers se régénèrent après le prélèvement des deux tendons semi-tendineux et gracile pour la reconstruction du LCA. La régénération des tendons n'était pas associée à la force de flexion isocinétique.

L'étude de biopsie humaine de greffe LCA in vivo présentée dans le **Chapitre 5** illustre l'histologie et la morphologie de l'autogreffe aux tendons ischio-jambiers dans diverses phases après une reconstruction du LCA réussie et une rééducation accélérée normalisée sans attelle. Il s'agissait d'un projet de recherche conjoint entre le Centre Médical Máxima (Eindhoven, Pays-Bas) et le Centre Charité de chirurgie de l'appareil musculo-squelettique (Berlin, Allemagne). L'hypothèse de l'étude était que les autogreffes aux tendons ischio-jambiers subissent un processus de remodelage qui adaptera leur aspect histologique à la morphologie de la LCA intacte et que ce processus sera complété après un an.

Chez soixante-sept patients, une biopsie a été prélevée de la partie centrale de la greffe après le succès clinique de la reconstruction du LCA par autogreffe aux ischio-jambiers. Les échantillons ont été attribués à l'un des trois groupes suivants, en fonction du point dans le temps du prélèvement: groupe 1 (6-12 mois; n = 15), groupe 2 (13-24 mois; n = 16) et groupe 3 (> 24 mois; n = 11). Les biopsies de tendons ischio-jambiers natifs (n = 17) et les LCA (n = 8) ont servi de témoins. La densité cellulaire, la densité vasculaire, la densité des myofibroblastes et l'alignement des fibrilles de collagène ont été analysés par l'hématoxyline-éosine, par le Trichrome de Masson-Goldner et par les protocoles de coloration immuno-histochimique.

L'étude a démontré que le nombre de cellules total avait augmenté, comparé aux tendons ischio-jambiers natifs (330,4/mm^2), a été augmenté dans les groupes 1-3 (groupe 1 = 482,0/mm^2 ($P = 0,036$); groupe 2 = 850,9/mm^2 ($P = 0,005$); et le groupe 3 = 595,6/mm^2 ($P = 0,043$)). Il n'y avait aucune différence significative entre les groupes pour la densité des vaisseaux.
La densité de myofibroblastes était plus élevée dans le groupe 2 (199,6/mm^2) comparé aux tendons ischio-jambiers natifs (1,9/mm^2, $P = 0,014$). Les myofibroblastes sont connus pour être des cellules importantes pour la cicatrisation des greffes LCA. Leur présence caractérise le remodelage actif de la greffe. La densité croissante des myofibroblastes entre 13 et 24 mois indiquait que le processus de remodelage chez l'homme dure plus longtemps que chez l'animal, au vu des résultats obtenus dans plusieurs études.

L'orientation de collagène a été irrégulière jusqu'à 12 mois. Par la suite, l'orientation de collagène est devenue plus régulière, avec un ajustement, mais sans rétablissement complet de la morphologie de la LCA initiale. Durant les 12 premiers mois, les cellules étaient principalement de forme ovoïde. La morphologie des cellules a ensuite changé en cellules fusiformes dans le groupe 2 et principalement en longues cellules étroites après 24 mois.

En conclusion, les greffes de tendons ischio-jambiers ont montré des étapes typiques de remodelage, qui n'ont pas été achevées jusqu'à 2 ans après la reconstruction du LCA. Le processus de remodelage chez l'homme a été prolongé par rapport aux résultats obtenus dans plusieurs études chez l'animal.

Le **Chapitre 6** décrit les connaissances actuelles sur le remodelage de greffe du LCA aux ischio-jambiers. Une comparaison est faite entre les données humaines et animales pour discuter des conséquences pour la rééducation. Une revue systématique de la littérature existante a été réalisée entre 1982 et 2012. Un accent particulier a été mis sur des études humaines et animales in vivo en analysant le remodelage de la greffe de tendon intra-articulaire.

Les études humaines et animales in vitro et in vivo ont montré qu'il existe trois étapes caractéristiques de cicatrisation de la greffe après une reconstruction du LCA : une phase de cicatrisation de la greffe précoce avec nécrose de la greffe centrale et hypocellularité et aucune revascularisation détectable du tissu greffé, suivie d'une phase de prolifération, la période de forte intensité de remodelage et de revascularisation et enfin, une phase de ligamentisation avec restructuration caractéristique de la greffe vers les propriétés d'origine du LCA. Cependant, une restauration complète des propriétés biologiques ou biomécaniques du LCA d'origine n'a pas été obtenue. Plus important encore, le processus de remodelage chez l'homme est plus long, comparé aux études chez l'animal. Alors que les protocoles de rééducation actuels sont souvent extrapolés à partir des résultats obtenus dans les études animales, les résultats actuels de l'homme dans les études in vivo pourraient nécessiter de nouveaux schémas postopératoires pour la reconstruction du LCA par autogreffe aux ischio-jambiers.

Les résultats cliniques et radiologiques à long terme après reconstruction du LCA par autogreffe aux ischio-jambiers avec rééducation accélérée sans attelle sont présentés au **Chapitre 7.** L'analyse a été effectuée en préopératoire et en postopératoire 10 ans après l'intervention dans une étude prospective de 100 patients. L'examen clinique a été mesuré à l'aide

des scores de Lysholm, de Tegner, les scores IKDC, les tests KT-1000 et les mesures de la circonférence de la jambe. L'évaluation radiologique incluait des clichés du genou suivants : AP portant, latéral, Rosenberg et rotule axiale. Les classifications radiologiques ont été réalisées selon Ahlbäck et Kellgren&Lawrence. L'analyse statistique incluait les régressions logistiques univariée et multivariée.

Les résultats ont montré une amélioration significative ($P < 0,001$) entre les mesures préopératoire et postopératoire pour les scores de Lysholm et Tegner, l'évaluation subjective du patient IKDC, les mesures KT-1000, la manoeuvre de McIntosh, le score IKDC et le test de saut sur une jambe ('one-leg hop'). Une manoeuvre de McIntosh positive ('glide' pivot shift) était encore présent chez 43 (50%) patients et corrélé avec des niveaux inférieurs d'activité ($P < 0,022$).
À 10 ans de suivi, des signes radiologiques d'arthrose étaient présents chez 53,5% des sujets. Le pourcentage d'arthrose après une méniscectomie et reconstruction du LCA était de 64,5% en comparaison à 20% dans le groupe avec reconstruction isolée du LCA. Les prédicteurs de l'arthrose étaient l'âge du patient ≥ à 30 ans au moment de la reconstruction du LCA, l'état du cartilage ≥ ICRS (International Cartilage Reseach Society – Société internationale de recherche du cartilage) grade 2 au moment de la reconstruction du LCA, l'histoire de la méniscectomie médiale et les tests de saut sur une jambe C et D en préopératoire. L'analyse de régression logistique multivariée a montré que l'état du ménisque médial et l'état du cartilage ICRS grade 3 au moment de la reconstruction du LCA étaient des prédicteurs importants de l'arthrose du genou. Une histoire de méniscectomie médiale avant ou au moment de la reconstruction du LCA augmentait de 4 fois le risque d'arthrose du genou (95% CI 1,41 à 11,5). Un grade ICRS 3 au moment de la reconstruction du LCA augmentait le risque d'arthrose du genou de 5,2 fois (95% CI 1,09 à 24,8). Le niveau d'activité (score Tegner ≥ 6) et une manoeuvre de McIntosh positive ne sont pas corrélés à l'arthrose.

En conclusion, la reconstruction transtibiale du LCA avec une autogreffe aux tendons ischio-jambiers à 4 brins et une rééducation accélérée sans attelle ont restauré la stabilité antéropostérieure du genou. Les paramètres cliniques et la satisfaction des patients ont été considérablement améliorés. Aucune preuve n'est donnée dans notre étude que la reconstruction du LCA empêchera l'arthrose du genou à long terme.

La discussion générale dans le **Chapitre 8** met l'accent sur la perspective actuelle de rééducation accélérée après reconstruction du LCA. Un nouveau modèle de recherche pour le remodelage de la greffe LCA termine ce chapitre.
Il est convenu que la cicatrisation de la greffe LCA ne peut progresser que si la charge mécanique se produit: cependant, l'ampleur la plus adéquate aux différents stades de cicatrisation n'est toujours pas déterminée.
La rééducation accélérée doit être aussi agressive que possible dans la restauration de la fonction tout en maintenant un environnement optimal de cicatrisation tissulaire.

Les objectifs des rééducations préopératoire et postopératoire, tels que définis dans le protocole normalisé de rééducation accélérée sans attelle de cette thèse (Annexe 1), sont cohérents avec les connaissances scientifiques actuelles sur la rééducation après reconstruction du LCA aux ischio-jambiers. Les recommandations pour de nouvelles améliorations sont: (1) la restauration de l'hyperextension préopératoire, le cas échéant; (2) les exercices du quadriceps en chaîne cinétique fermée sont préférables durant les 12 premières semaines de la rééducation. Commencer ces exercices en génuflexion de 50°-90°, et augmenter progressivement le mouvement jusqu'à 0°-90° avec la résistance tolérable par le patient. La génération de fatigue bilatérale améliore la symétrie de charge dans les exercices en chaîne cinétique fermée; (3) une combinaison d'exercices de quadriceps en chaîne cinétique fermée et en chaîne cinétique ouverte est recommandée. Il est plus sûr de commencer les exercices de quadriceps en chaîne cinétique ouverte à 12 semaines à 0°-90°, en ajoutant des exercices concentriques et excentriques progressifs à 13 semaines. L'entraînement excentrique est recommandé pour les exercices de renforcement du quadriceps avec l'accent sur la formation des deux jambes; (4) la synovie du genou doit guider le rythme de rééducation et; (5) se concentrer sur la qualité du mouvement, comme le valgus dynamique du genou, est important dans la rééducation du LCA.

Cette thèse a montré que, malgré les nombreuses publications sur le sujet, il n'existe pas actuellement de lignes directrices pour déterminer quand un retour en toute sécurité à l'activité sera possible sans restriction. Les études en cours de validité, fondées sur des critères d'évaluations pour déterminer la préparation d'une formation spécifique au sport, sont nécessaires et offrent des possibilités pour poursuivre les recherches. Identifier les phénotypes de patients spécifiques, éventuellement liés au sexe, pourrait permettre une approche de rééducation plus personnalisée.
Les études identifiant les différences propres aux sports, dans les résultats de reconstruction du LCA chez les athlètes, pourraient renforcer les différentes échelles de temps de rééducation après une reconstruction du LCA.

Les similitudes frappantes entre les modèles de cicatrisation de tendinopathie et le remodelage de la greffe aux tendons ischio-jambiers ont inspiré ma réflexion de recherche d'un nouveau modèle pour le remodelage du LCA et la rééducation. Compte tenu de la faculté d'adaptation du tendon à la charge et de l'effet de plafond dans la synthèse du collagène par les fibroblastes, il serait intéressant d'étudier le développement de stratégies préopératoires pour augmenter la teneur en collagène dans les tendons ischio-jambiers avant leur utilisation comme greffes de LCA. Cela pourrait augmenter la force de la greffe de tendon du LCA et éventuellement diminuer les taux de rupture de greffes du LCA dans des activités liées au sport.

Les femmes présentent moins d'augmentation de la synthèse de collagène, ont besoin de plus de temps pour l'adaptation du tendon à la charge et sont plus sensibles aux blessures (nouvelles) du tissu mou que les hommes. Cette synthèse de collagène liée aux oestrogènes peut nécessiter des stratégies de rééducation différentes pour les hommes et les femmes pour la cicatrisation optimale d'une greffe du LCA. De futures recherches comparatives entre les sexes pourraient conduire à de meilleurs résultats après une reconstruction du LCA.

La prédisposition génétique semble liée au développement d'une tendinopathie. Les variantes génétiques modifient les tendons jusqu'à perturbation de la matrice et affaiblissent la force des tendons. Fait intéressant, les gènes codant pour ces protéines ont également été associés à une rupture du LCA. Ceci offre une autre opportunité de recherche pour déterminer si les patients génétiquement à risque accru de tendinopathie ont également plus souvent de nouvelles ruptures après reconstruction par autogreffe aux tendons ischio-jambiers. Si oui, ces patients pourraient bénéficier d'allogreffes de tissus au lieu d'autogreffes de tendons comme la greffe du LCA.

Les études de biopsie dans cette thèse ont montré que les structures périphériques de l'autogreffe aux tendons ischio-jambiers passent par des phases typiques de remodelage semblables aux modèles de la pathogenèse de la tendinopathie. Le centre de la greffe semblant être moins impliqué dans la cicatrisation et la force dans la tendinopathie, la prévention de néovascularisation et la croissance pathologique des nerfs dans la greffe de tendon LCA est un nouveau domaine de recherche. Cela pourrait offrir de nouveaux horizons pour un traitement optimal et des résultats après une reconstruction du LCA. Les techniques d'imagerie pour la tendinopathie peuvent surveiller le traitement et les effets biologiques dans les phases de remodelage des greffes de LCA par une charge en temps et dose spécifiques de différentes modalités de rééducation.

En résumé, la recherche future devrait être consacrée à: (1) l'optimisation des reconstructions du LCA visant à rétablir complètement l'anatomie et la fonction tout en conservant la résistance mécanique du LCA intact; (2) l'élaboration d'options de traitement biologiques influant sur la greffe, en particulier au cours de la phase précoce et de la prolifération, pour optimiser le remodelage de la matrice extracellulaire et éviter une activité excessive de remodelage, qui pourrait nuire à l'intégrité mécanique de la cicatrisation de la greffe et; (3) afin de mieux différencier les «bons» des «mauvais» changements de remodelage, de manière à pouvoir réduire le temps de retour à un sport sans aucune restriction.

APPENDIX I. STANDARDIZED ACCELERATED REHABILITATION PROTOCOL

Outline of the standardized brace-free accelerated rehabilitation protocol after ACL reconstruction with hamstring tendon autografts (used in all studies of this thesis – protocol 1997)

General principles

- No immobilization or brace after surgery. Full weight-bearing as tolerated by pain. Crutches are discarded when the patient regains a normal gait pattern.
- Five phases of rehabilitation. Transition to the next phase occurs after meeting the goals of the previous phase. Each phase has specific considerations for ROM (range of motion), neuromuscular and strengthening exercises. Symptoms of pain and swelling of the knee should guide rehabilitation.
- The neuromuscular programme consists of proprioceptive (= afferent) and coordination (= efferent) exercises.
- Open kinetic strengthening exercises are allowed after 8 weeks postsurgery, but closed kinetic exercises are preferred. The quality of performance is important.
- Physiotherapy guidance until the desired level of activity is achieved.
- Outpatient clinic appointments with the orthopaedic surgeon at 2 weeks, 6 weeks, 4–6 months and 1 year after surgery. Additional appointments are made if deemed necessary.
- Patient reported outcome measures (PROM) recorded preoperatively, at 4–6 months and 1 year after ACL reconstruction (Tegner-, Lysholm-, IKDC-scores, KT-1000).
- Return to sports is allowed after 4 months.
- Concomitant surgery or injuries may need specific adaptations in the ACL rehabilitation.

Phase 1. Prehabilitation (preoperative phase)
Patient information on surgical procedure, rehabilitation and expectations.

- **Weight-bearing:** Unrestricted. Instructions and training to walk with crutches.
- **ROM:** Full patellofemoral and tibiofemoral ROM.
- **Neuromuscular:** Gait optimization. Static and dynamic exercises.
- **Strengthening:** Open and closed kinetic chain exercises for gluteus, quadriceps, hamstrings and gastrocnemius muscles. Unlimited cycling.

Goals: Normal gait. Full ROM. Quadriceps Limb Symmetry Index (LSI) < 20%. Reduction of knee swelling if present. Realistic patient expectations.

Phase 2. Limited loading ADL (activities of daily living) phase (0–4 weeks)
Day of surgery: No immobilization or brace. Cryotherapy, isometric quadriceps and extension exercises in bed, adequate pain control.

Day 1:

- **Weight-bearing:** As tolerated with two crutches. Full weight-bearing allowed.
- **ROM:** Flexion/Extension (F/E) 90–0–0° in closed kinetic chain. Passive exercises by physiotherapist and continuous passive motion (CPM) if necessary. Passive and active extension exercises. Patella mobilization. Cryotherapy after exercises.
- **Neuromuscular:** Gait optimization. Stair climbing exercises. Simple static exercises.
- **Strengthening:** Isometric quadriceps, hamstrings and gastrocnemius exercises.

Goals at discharge: ADL independency, ROM F/E 90–0–0°, normal gait and stair climbing with crutches.

Day 2–14:
Physiotherapy in outpatient setting 2–3 times per week. Cryotherapy if needed.

- **Weight-bearing:** As tolerated with two crutches. Full weight-bearing allowed. Crutches are discarded if the patient has sufficient neuromuscular control and a normal gait pattern (usually 1–3 weeks postoperatively).
- **ROM:** F/E 120–0–0°.
- **Neuromuscular:** Gait optimization. Simple static exercises.
- **Strengthening:** Closed kinetic chain quadriceps, hamstrings and gastrocnemius exercises. Cycling 60–80 RPM, start 25 Watt. Hip rehabilitation (abduction, adduction, flexion and extension exercises)

Goals at 2 weeks: Adequate wound healing, ADL independency and active ROM F/E 90–0–0°.

Weeks 2–4:

- **Weight-bearing:** Full weight-bearing. Crutches are discarded if the patient has sufficient neuromuscular control and a normal gait pattern (usually 1–3 weeks postoperatively).
- **ROM:** F/E 120–0–0°. Increase ROM using (stationary) bicycle, twice daily for 10–15 minutes. Lower the seat as flexion increases.
- **Neuromuscular:** Gait optimization. Progressive static exercises after 3 weeks.
- **Strengthening:** Closed kinetic quadriceps, hamstrings and gastrocnemius exercises. Cycling gradual increase from 60–90 RPM and 25 to 125 Watt. Hip rehabilitation (passive and active: abduction, adduction, flexion and extension exercises). Unlimited walking distance and swimming as comfort permits.

Goals phase 2: ROM F/E 120–0–0°. Full active and passive knee extension with dynamic gait. Resume light work/office job.

Phase 3. Loading ADL phase (4–10 weeks)
Considerations in rehabilitation: at 6 weeks postsurgery, ACL graft at its weakest due to active remodelling (data extrapolated from animal studies).

- **Weight-bearing:** Full weight-bearing.
- **ROM:** Full ROM. Increase ROM using (stationary) bicycle, twice daily for 10–15 minutes. Lower the seat as flexion increases. Active flexion and extension exercises if necessary.
- **Neuromuscular:** Gait optimization. Static and dynamic exercises.
- **Strengthening:** Functional training (squat/squat lunge/deadlift/wall sits/step ups-downs). Closed kinetic chain quadriceps and hamstrings exercises. From week 6: add open kinetic chain quadriceps exercises between maximum flexion and 50 degrees. Build endurance (cycling, cross trainer, rowing machine). Cycling 90 RPM, gradual increase to 175 Watt.

Goals phase 3: Full ROM. Normal gait in ADL. Minimal swelling after training. Able to perform static and light dynamic neuromuscular exercises. Hamstring strength LSI 70–90% of contralateral leg. Quadriceps strength 60–70% of contralateral leg (hop-test control). Jogging, golf, shooting baskets, running (forward and backwards, sideways) and cross-overs. Resume heavy labor.

Phase 4. Loading sports phase (10–16 weeks)

- **Weight-bearing:** Full weight-bearing.
- **ROM:** Full ROM.
- **Neuromuscular:** Focus on dynamic exercises, jumping and perturbation training. Gait optimization in running.
- **Strengthening:** Progressive functional strength and endurance training. Concentric and eccentric quadriceps exercises in full ROM. Cycling 90 RPM, 200 Watt. Start sport-specific training if quadriceps and hamstring LSI < 20%.

Goals phase 4: Active dynamic gait in running activities. Able to perform extensive neuromuscular exercises (trampoline, gyrosphere, drills with perturbation and slalom). Quadriceps and hamstring LSI < 10%. Return to unrestricted activities and noncontact sports.

Phase 5. Sport-specific training phase (4–6 months)

- **Weight-bearing:** Full weight-bearing.
- **ROM:** Full ROM.
- **Neuromuscular:** Sport-specific dynamic exercises.
- **Strengthening:** Sport-specific strength and endurance training.

Goals phase 5: Return to unrestricted contact sports.

APPENDIX II. PUBLICATIONS CONTRIBUTING TO PHD THESIS

Janssen RPA, Scheffler SU (2016) Graft remodeling & ligamentization after ACL reconstruction. In Prodromos et al. Eds. The Anterior Cruciate Ligament: Reconstruction and Basic Science. 2nd ed. Saunders, an imprint of Elsevier, Inc.

Janssen RPA, Reijman M, Janssen DM, Mourik van JBA (2016) Vascular complications after ACL reconstruction and DVT prophylaxis. In Prodromos et al. Eds. The Anterior Cruciate Ligament: Reconstruction and Basic Science. 2nd ed. Saunders, an imprint of Elsevier, Inc.

Janssen RPA, Reijman M, Janssen DM, Mourik van JBA (2016) Arterial complications, venous thromboembolism & DVT prophylaxis after ACL reconstruction. A systematic review. World J Orthop (submitted)

Janssen RPA, Engelen-van Melick N, Mourik van JBA, Reijman M, Rhijn van LW (2016) Anterior cruciate ligament reconstruction and accelerated brace-free rehabilitation: a systematic review. Part I. Hamstring tendon autograft. Eur J Phys Rehab Med (submitted)

Janssen RPA, Engelen-van Melick N, Mourik van JBA, Reijman M, Rhijn van LW (2016) Anterior cruciate ligament reconstruction and accelerated brace-free rehabilitation: a systematic review. Part II. Patellar tendon versus hamstring tendon autograft. Eur J Phys Rehab Med (submitted)

Huang H, Horemans H, Keijsers N, **Janssen RPA**, Stam H, Praet S (2015) Dynamic pedobarography to evaluate gait symmetry after anterior cruciate ligament reconstruction. CORR (submitted)

Janssen RPA, Velden van der MJF, Besselaar van den M, Reijman M (2015) Prediction of length and diameter of hamstring tendon autografts for knee ligament surgery in Caucasians. Knee Surg Sports Traumatol Arthrosc 2015 Jun 28. [Epub ahead of print]. DOI: 10.1007/s00167-015-3678-5

Arts SJ, Polak MPJ, **Janssen RPA** (2015) Anterior cruciate ligament regeneration in an 8-year-old patient. J Knee Surg Rep 00:1-4

Brooymans FAM, Lenssen AF, Engelen-van Melick N, Neeleman-vder Steen CWM, Rondhuis G, Moorsel v SR, Hullegie W, Hendriks HJM, **Janssen RPA** (2015) Evidence Statement "Acuut Knieletsel". Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF)

Janssen RPA, Scheffler SU (2014) Intra-articular remodelling of hamstring tendon grafts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 22:2102-2108

Janssen RPA, Scheffler SU (2014) Remodeling of hamstring tendon grafts after ACL reconstruction. In Siebold, Dejour, Zaffagnini, Eds. Anterior Cruciate Ligament Reconstruction – A Practical Surgical Guide. 1st ed. Springer

Engelen-van Melick N, Brooymans FAM, **Janssen RPA** (2014) Revalidatie na voorste-kruisbandreconstructie. Bohn Stafleu van Loghum (Springer Media), Houten

Janssen RPA, Velden vder MJF, Pasmans HLM, Sala HAGM (2013) Regeneration of hamstring tendons after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 21: 898-905

Janssen RPA, Du Mée AWF, Valkenburg v J, Sala HAGM, Tseng CM (2013) Anterior cruciate ligament reconstruction with hamstring tendons and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. Knee Surg Sports Traumatol Arthrosc 21:1977-1988

Janssen RPA, Wijk vder J, Fiedler A, Schmidt T, Sala HAGM, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19:1299-1306

Janssen RPA (2011) Beschermt een voorste kruisbandreconstructie tegen knie-artrose? Physios 3:23-30

Janssen RPA (2008) Vascular complications after anterior cruciate ligament reconstruction. In Prodromos CC, ed. The Anterior Cruciate Ligament: Reconstruction and Basic Science. 1st ed. Saunders an imprint of Elsevier, Inc.

Janssen RPA, Sala HAGM (2007) Embolism of the popliteal artery after anterior cruciate ligament reconstruction: a case report and literature review. Knee Surg Sports Traumatol Arthrosc 15:1449-1451

Janssen RPA, Sala HAGM, Prakken WJ (2007) Simultaneous traumatic pseudoaneurysm and thrombosis of the popliteal artery after anterior cruciate ligament reconstruction. Injury Extra 38:397-399

Janssen RPA, Sala HAGM (2007) Fatal pulmonary embolism after anterior cruciate ligament reconstruction. Am J Sports Med 35:1000-1002

Janssen RPA, Scheltinga MRM, Sala HAGM (2004) Pseudoaneurysm of the popliteal artery after anterior cruciate ligament reconstruction with bicortical tibial screw fixation. Arthroscopy 20:E4-6

Full list of publications by Rob P.A. Janssen @ www.rpajanssen.com

APPENDIX III. VALORISATION

Introduction
This valorisation appendix describes the innovative, economic and social implications of new knowledge on anterior cruciate ligament (ACL) reconstruction & accelerated rehabilitation in this thesis.

Innovation
The most important finding of this thesis is that current biological evidence on graft healing does not support return to unrestricted sports at 4-6 months after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. The remodelling process in humans is prolonged compared to animal studies. While today's rehabilitation protocols are often extrapolated from findings in animal studies, the findings of human in vivo studies in this thesis might require new postoperative regimens following hamstring tendon ACL reconstruction. Graft healing is a prolonged process, which is still active after 1 year. This knowledge allows physicians and physiotherapists to better inform patients on the expected time course of rehabilitation after ACL reconstruction and to present realistic expectations for a safer return to sports. I am proud that these studies have had considerable impact in sports medicine and ACL rehabilitation.

Patients are frequently referred by physiotherapists, sports physicians and other physicians for ACL reconstruction to "prevent" long-term knee osteoarthritis. This thesis has shown that there is a significant improvement of clinical parameters and patient satisfaction after hamstring tendon ACL reconstruction with accelerated brace-free rehabilitation. However, it was also demonstrated that ACL reconstruction does not prevent long-term knee osteoarthritis: at 10-year follow-up, radiological signs of osteoarthritis were present in 53.5 % of patients. Persons with risk factors for osteoarthritis as defined in this thesis should be made aware of their even higher risk of osteoarthritis. Emphasis on timely adaptation of their sports activities could limit long-term knee osteoarthritis. More importantly, health care professionals should be conscious of the fact that an ACL reconstruction does NOT prevent knee osteoarthritis.

Accelerated brace-free rehabilitation starts preoperatively and should emphasize full knee range of motion, gait training and quadriceps limb symmetry index < 20% before surgery. After surgery, a progressive scheme of function, strength and neuromuscular training allows patients to advance as they achieve quantifiable goals.

The goals of pre- and postoperative rehabilitation, as defined in the standardized accelerated brace-free rehabilitation protocol of this thesis (Appendix 1), cohere with current scientific views on hamstring tendon autograft ACL rehabilitation. This thesis presents recommendations for further improvements that will help physiotherapists to treat patients with evidence based ACL rehabilitation protocols.

This thesis has shown that hamstring tendons regenerate in the upper leg after harvest for ACL reconstruction. There was no correlation between tendon regeneration and isokinetic flexion strength. One might consider the possible use of these regenerated hamstring tendons for complex or revision knee ligament surgery. Further histological research is recommended to analyse this innovative concept.

Economic and social relevance
Playing sports is healthy but may also lead to various types of injuries. Sport is defined as a physical activity in a performance setting when an achievement is considered to be important.[1]
In 2013, 4.5 million sports injuries occurred in The Netherlands, of which 1.9 million (42%) required medical treatment by various health care professionals (Table 1). Sports caused nearly half (47%) of the 4 million medically treated traumatic injuries in The Netherlands in 2013. Four out of ten sports injuries (38%) needed medical treatment in 2014. Furthermore, sports injuries limit sports participation and interfere with sport-health benefits.[2]

Table 1 Sports injuries in The Nederland 2013[2]

	Number of injuries	Number of treatments
All injuries	4.500.000	
Medically treated injuries	1.900.000	
Physiotherapist	1.100.000	7.300.000
General physician	820.000	1.100.000
Medical specialist	380.000	950.000
Emergency department hospital	130.000	
Sports physician	150.000	
Hospital admissions	12000	
Deceased	29	

In The Netherlands, the number of injured sports participants has increased from 29% in 2007 to 38% in 2014. A total of 4.7 million sports injuries were registered in 2014, 200.000 more than in 2013, with an increase of 29% in comparison to 2006. The rise in sports injuries is greater than the rise in sports participants. There is also an increase in risk of sports injuries (number of injuries per 1000 hours of sports participation): 2.1 injuries per 1000 hours in 2014 compared to 1.8 in 2006. Football (soccer), running and fitness cause most sports injuries. These three sports are popular in The Netherlands.[3]

More than 2/3 of sports injuries (69%) have a sudden onset. Runners have the greatest risk of injury but football was responsible for the majority of sports injuries in 2013 (760.000) as well as most knee injuries in both men and women.[2] The majority of patients treated for knee injuries in emergency departments was 10-24 years of age (64%). Knee ligament injuries by non-contact trauma constituted 31% of all knee diagnosis.[4] This trauma mechanism is the most frequent cause for an ACL rupture. Medical costs per knee injury are estimated at € 980 and knee injuries often lead to relatively frequent and long nuisance for patients.[2]

Sports injuries lead to social and economic costs, estimated at € 1.5 billion per year in The Netherlands. Absence from work constitutes 2/3 of these costs (€ 1 billion). The remainder 1/3 (€ 520 million) are direct medical costs for treatment at emergency departments, hospital admissions, physiotherapy and physician expenses. These costs for sports injuries still outweigh the medical costs caused by insufficient physical activity, estimated at € 907 million.[2]

The Dutch government invests € 675.000 per year from 2016-2020 to counter the increasing number of sports injuries. Measures will focus on sports with most frequent injuries (football, running and fitness) as well as validated prevention programmes of sports injuries.[3]
This government prevention programme mainly focuses on sports circumstances. Field conditions, sports frequency, training conditions, nutrition and other external factors are important, however one needs to realize that 24% of all knee injuries are a recurrence of a previous injury.[4]
As such, the focus on optimal rehabilitation after ACL injury or ACL reconstruction for a safe return to play is also valuable to decrease the amount of sports injuries. This thesis has shown that the development of valid, criterion-based assessments to determine readiness for sport-specific training and eventual return to sports is greatly needed and offers opportunities for further research. Identifying specific patient phenotypes, possibly gender-related, may allow a more customized rehabilitation approach. This thesis recommends new studies to identify sport-specific differences in ACL reconstruction outcomes in athletes that could further enhance different time frames of rehabilitation after ACL reconstruction. These novel insights might reduce the number of knee sports (re)injuries, initiate safer return to sports and stimulate sports enjoyment with accompanying health benefits. This will further ensue a decrease in absence of work, less medical costs and therefore lower economic costs related to sports injuries.

This thesis has shown that the length and diameter of hamstring tendon autografts can be predicted based on antropometric parameters. This is cost effective in complex knee ligament surgery because it reduces the need for expensive allograft use. The use of more autografts for knee ligament surgery allows for better quality of ligament reconstructions, hence less reinjury rate and less economic costs. It also facilitates reliable surgical procedures in countries where allografts are not available.

Target group
The results of this thesis are relevant for various health care professionals: orthopaedic surgeons, trauma surgeons, sports physicians, physiotherapists and general physicians. Adequate indications for surgery, essence of prehabilitation, surgical technique, knowledge on rehabilitation and long-term risk of osteoarthritis will allow the physician and physiotherapist to present state of the art treatment for ACL reconstructed patients with hamstring tendon autografts.

Policymakers working for local or (inter)national sports and government organizations may benefit from the knowledge presented in this thesis. The current programmes to stimulate football among girls and women should consider the 2-9x higher risk of an ACL rupture in women compared to men.[5,6] This thesis has shown that an ACL reconstruction does not prevent long-term osteoarthritis of the knee. ACL injuries in female athletes can have detrimental consequences on overall wellbeing, contribute to chronic knee problems, and impair future sports involvement.[6] If a girl ruptures her ACL at age 15, this thesis has shown that there is a considerable chance that she might develop knee osteoarthritis by her late 20's. Policymakers should take into account the long-term risk and social implications of sports stimulation in specific patient populations.

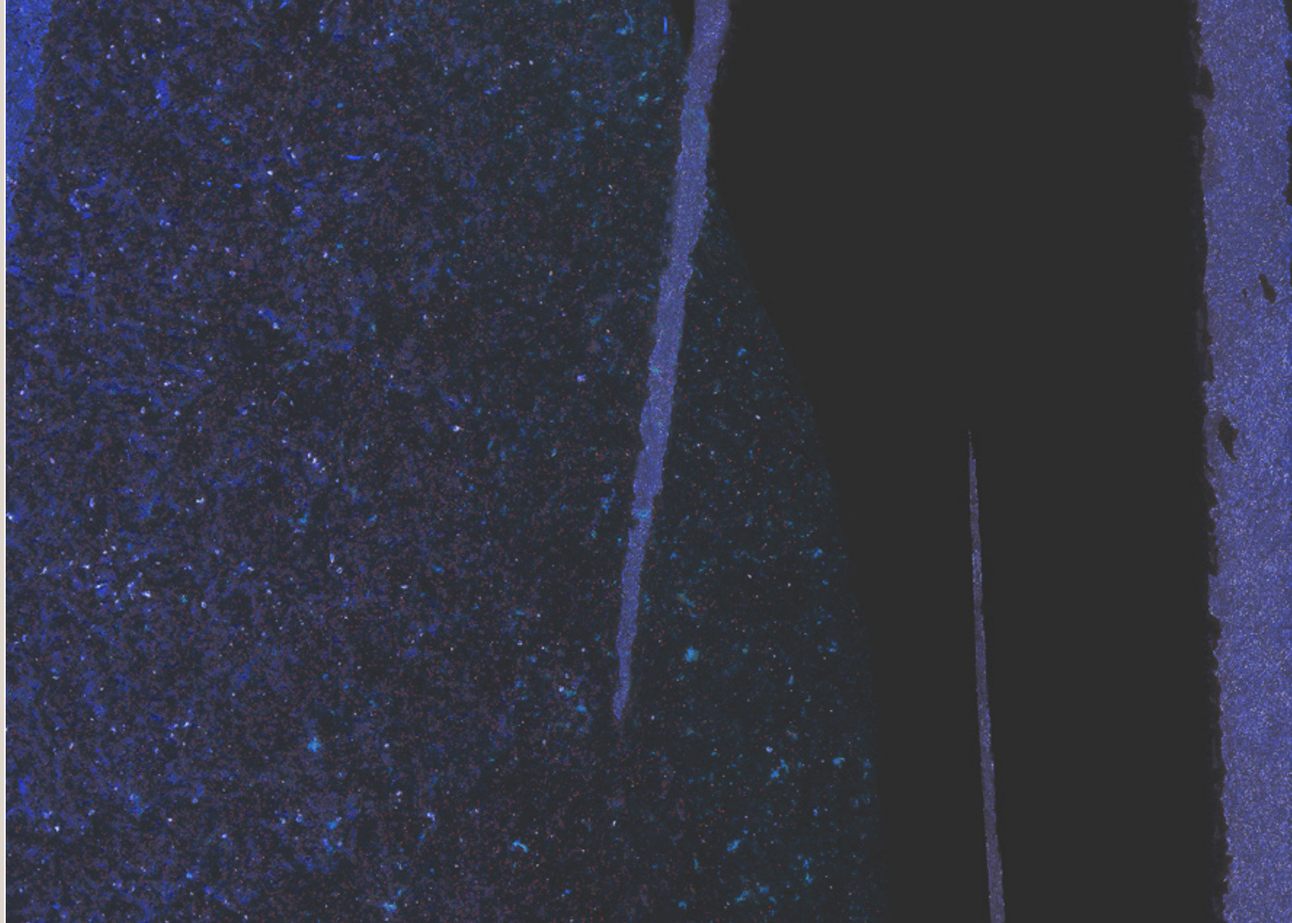
Sports coaches may also benefit from the knowledge of this thesis. There is promising evidence that female knee injury patterns can be prevented and corrected by participation in an ACL prevention programme.[6] The ideal ACL prevention programme incorporates exercises and drills that emphasize plyometrics, neuromuscular training, and muscle strengthening, as well as education and feedback regarding body mechanics and landing technique. This thesis has emphasized the importance of focus on quality of movement, such as dynamic knee valgus in ACL rehabilitation. It would ideally begin 6 weeks prior to the season, can be as short as 20 minutes, and can be done instead of a typical warm-up.[6] These programmes could also be institutionalized in schools or sports clubs in the Netherlands for girls playing pivoting sports such as football, field hockey and indoor sports to reduce the short- and long-term consequences of ACL knee injuries. Creating prevention programmes that also simultaneously enhance sports performance can further motivate coaches and athletes to participate on a larger scale.[6]

Future research

Analysis of the biological effects in the remodelling phases of ACL grafts by time- and dose-specific loading of different rehabilitation modalities could improve rehabilitation protocols for safe return to sports. However, human in vivo biopsy studies are ethically difficult to perform. This thesis has shown that biopsy studies of the peripheral structures of the hamstring tendon ACL autograft show typical phases of remodelling similar to the pathogenesis models of tendinopathy. As the centre of the graft seems to be less involved in healing and strength in tendinopathy, prevention of neovascularization and pathological nerve ingrowth into the ACL tendon graft is a new area for research. This might offer new horizons for optimal treatment and outcome after ACL reconstruction. New imaging techniques for tendinopathy may monitor treatment and biological effects in the remodelling phases of ACL grafts. This research may generate new patents for imaging techniques for ACL graft remodelling.

References

1. Nationaal Kompas Volksgezondheid, 23 juni 2014. RIVM, Bilthoven
2. Sportblessures. Blessurecijfers – VeiligheidNL – april 2015
3. Minister mw. drs. E.I. Schippers. Nieuw programma sportblessurepreventie. Kamerbrief 26 mei 2015
4. Knieblessures. Blessurecijfers – VeiligheidNL – juni 2013
5. Ageberg E, Forssblad M, Herbertsson P, Roos EM (2010) Sex differences in patient-reported outcomes after anterior cruciate ligament reconstruction: data from the Swedish knee ligament register. Am J Sports Med 38(7):1334-1342
6. Voskanian N (2013) ACL Injury prevention in female athletes: review of the literature and practical considerations in implementing an ACL prevention program Curr Rev Musculoskelet Med 6(2): 158–163



Acknowledgements · Dankwoord

"Heb je al een datum?" Die vraag is mij het meest gesteld in de afgelopen jaren als het onderwerp promotie aan bod kwam. De lat ligt hoog, ook in het schrijven van het proefschrift. Het duurt even, maar dan heb je ook wat... Ik ben heel veel mensen dankbaar voor hun interesse tijdens al die jaren en ik zou een aantal in het bijzonder willen benoemen.

Mijn promotor: Prof.dr. L.W. van Rhijn, beste Lodewijk, jouw wetenschappelijke finesse en persoonlijke betrokkenheid hebben diepe indruk op mij gemaakt. Onze besprekingen waren intensief en stimulerend. Je gaf mijn promotietraject de juiste richting om mijn ambities waar te maken en ik ben je zeer dankbaar voor je begeleiding en het mogen behouden van mijn eigen stijl. Ik verheug me op onze verdere samenwerking in de opleiding orthopedie en de wetenschap.

Mijn copromotor: dr. J.B.A. van Mourik, beste Jan, woorden schieten tekort om jou te bedanken voor jouw rol als initiator, organisator, aangenaam kritisch begeleider, en bovenal je interesse in mijn promotie. Ik ben trots dat je mijn copromotor bent en bewonder je integriteit.
Ik wil Elly en jou danken voor jullie onvoorwaardelijke steun.
Yin-Yang, de cirkel is rond: ik beschouw het als een grote eer dat ik het opleiderschap mag overnemen van mijn eigen opleider.

Leden van de promotiecommissie: Prof.dr. R.A. de Bie, Prof.dr. R.L. Diercks, Prof.dr. I.C. Heyligers, Prof.dr. G.M.M.J. Kerkhoffs, Prof.dr. N.L.U. van Meeteren, dr. P.J. Emans en dr. E.J.P. Jansen, dank u wel voor uw oordeel, tijd en betrokkenheid.

Design, kunst en creatieve geesten: Rhea Strik & Tayfun van Zantvoort. Samen de drie musketiers, out of the box, vorm en inhoud, medisch & kunst, kabouters, Lisa's meesterproef, diepe gelaagdheid en ongekende hoogte. Niemand kent de diepgang van dit boek beter dan jullie. Gracias!

Drukwerk: Leo Peters, ik heb je grote toewijding in de realisatie erg gewaardeerd, dank je wel.

Mijn paranimfen: Roel en Ruud, drie citaten symboliseren onze bijzondere vriendschap:

"What we do for ourselves, dies with us.
What we do for the world and others remains immortal" – Albert Pine.
"Don't play what's there, play what's not there" – Miles Davis.
"After you've done all the work and prepared as much as you can, what the hell, you might as well go out and have a good time" – Benny Goodman.

Merci beaucoup mes amis ... bedankt hè!!

Mijn wetenschappelijke 'godfather': dr. Joost Vegter, ik ben je zeer erkentelijk voor het scheppen van de juiste kaders om mijn liefde voor wetenschap te laten ontwaken in 1996. "Rob, dit weekend ga je in bad zitten en nadenken over remodellering" was één van je visionaire adviezen. Kadreren is je kracht, ook symbolisch voor je prachtige fotografie. Ik probeer jouw stimulans voor wetenschap met evenveel enthousiasme over te brengen op mijn opleidingsassistenten.

De mede-initiatoren: H.A.G.M. Sala en Prof.dr. R.G.T. Geesink.
Beste Harm, jij speelt een sleutelrol in dit werk. Jouw bevlogenheid over dit onderwerp vormen de basis voor onze publicaties en mijn gespecialiseerde knielpraktijk. Dank je wel voor alle wijze lessen over de knie, het leven en zelfs sport!
Beste Ruud, de duur van mijn promotietraject en jouw emiraat als hoogleraar orthopedie hebben elkaar gekruist. Mijn grote dank voor het leggen van het fundament waarop dit proefschrift is gebouwd.

Mijn Nederlandse co-auteurs: Harm Sala, Marly van der Velden, dr. Max Reijman, Nicky Engelen-van Melick, dr. Jan van Mourik, prof.dr. Lodewijk van Rhijn, Marijn van den Besselaar, Huub Pasmans, Jasper van der Wijk, Arthur de Mée, Juliette van Valkenburg en Carroll Tseng, jullie bijdragen zijn van grote waarde voor dit proefschrift. Ik ben erg dankbaar voor jullie betrokkenheid, bereidheid om tegenslagen aan te pakken en de vele uren die jullie aan onze publicaties hebben besteed. Dr. Ineke van Lijnschoten en dr. Saskia Houterman, ook jullie bijdragen heb ik erg gewaardeerd.

My international co-authors:
PD Dr. med. S.U. Scheffler, dear Sven, thank you very much for your vision on graft remodelling, boundless efforts and warm friendship which have turned our ACL projects into life long experiences. I enjoy our mutual interest in the fundamentals of sports medicine and look forward to more joint adventures. Thank you again.
Dr. med. vet. T. Schmidt and A. Fiedler, dear Tanja and Anja, our research on human ACL graft remodelling was very special to me. Great science and wonderful culinary and night-time discoveries in Berlin. I am very proud of your achievements and the impact that our studies have had in sports medicine. Vielen Dank!

De patiënten: zonder alle mensen die deelnamen aan de klinische studies van dit proefschrift was het werk nooit gelukt. Ik ben u allen zeer erkentelijk voor uw bereidheid om de wetenschap een stap vooruit te helpen.

PhD coördinator School CAPHRI & orthopedie MUMC+:
dr. Hannerieke van der Boom en Jerney Willems, dank jullie wel voor het efficiënt en enthousiast meesturen in de afrondende fase van mijn proefschrift.

Leden Coöperatie Orthopedie Groot Eindhoven: Anouk, Janneke, Kathleen, Jan, Florens, Arnold, Hans, Marijn, Robin, Willem, Henk, Coen, Kees, Paul, Niek, dank voor jullie collegialiteit en ondersteuning van mijn wetenschappelijke interesse. Het begeleiden van onze twee fusies heeft de datum wat vertraagd, maar ook die investering was alle moeite waard. Ik ben trots op COGE!

Collega's Máxima Medisch Centrum Eindhoven-Veldhoven:
Kennis & Informatiecentrum: Eugenie Delvaux & Bart de Vries, ik heb jullie service en betrokkenheid erg gewaardeerd, niets was teveel!
MMC Academie: dr. Jeanne Dieleman, dank voor de steun voor mijn proefschrift en de wetenschap orthopedie & traumatologie in het MMC.
Orthopedie: (oud)-AIOS orthopedie, "werk is interessant, leuk is voor thuis & wetenschap" ☺ Alle medewerkers orthopedie polikliniek, operatiecomplex, afdelingen en cORTHEx: dank voor jullie geduld, bijdrage en interesse in mijn proefschrift.

Communicatie en social media: Cintha & team, jullie zijn geweldig, excelleren mag!
Medisch specialisten en raad van bestuur: ik vind het plezierig om in een ziekenhuis te werken waar wetenschap en opleiding als kernwaarden worden gezien. In het bijzonder dank ik dr. Marc Scheltinga voor de samenwerking in het MMC tertiair verwijscentrum voor complexe kniechirurgie.

Nederlandse Vereniging voor Arthroscopie – NVA: ik dank het bestuur en Odette de Beer voor hun interesse en ondersteuning van mijn proefschrift. Lid zijn van de NVA weerspiegelt nieuwsgierigheid naar innovatie en kwaliteit van artroscopisch handelen. Ik kijk uit naar een blijvende samenwerking in wetenschap en onderwijs. Lieve Odette, het was een feest om met je te mogen samenwerken. Ik ben trots dat Gino Kerkhoffs mijn opvolger is en ik wens hem net zoveel plezier en voldoening als dat ik heb mogen ervaren als voorzitter van deze prachtige vereniging.

Organiserend comité Arthroscopy & Arthroplasty Course Utrecht:
al 27 jaar de beste onafhankelijke arthroscopiecursus in Nederland en inmiddels ook internationaal beroemd. Ik heb diep respect voor de visie en de inzet van dr. Jaap Willems, dr. Arthur Lim, Florence en Jacqueline in al die jaren. Ik dank alle comitéleden en sponsoren, in het bijzonder mijn Advanced Knee Course maatjes Michiel van Haeff, Ton van Loon, MaTThijs Somford en Reinoud Brouwer voor het jaarlijks hoogtepunt in overdracht van kennis, chirurgische technieken en wetenschap. Ik vind het een grote eer om het A&A voorzitterschap over te nemen in 2016 en heb veel vertrouwen in dit krachtig comité om de cursus de tand des tijd te laten doorstaan.

ATLS® Nederland: mijn 'roots' voor onderwijs en bestuurlijke activiteiten liggen bij jullie. Ik dank het bestuur, mijn mede-instructeurs en alle huidige en oud-medewerkers voor dit stevig fundament sinds 2002. Ik ben van mening dat ATLS® Nederland een belangrijke voedingsbodem zal zijn voor de gezamenlijke traumatologie in Nederland.

Financiële partners: naast de NVA en MMC Academie ben ik de Nederlandse Orthopaedische Vereniging (NOV) en de Stichting AA Wetenschap en Onderwijs erkentelijk voor de financiële bijdragen aan mijn proefschrift.

Inspiring persons:
Er zijn een aantal bijzondere mensen die mij blijven inspireren:

Prof.dr. G.M.M.J. Kerkhoffs, beste Gino, onze inspirerende paden kruisen elkaar steeds vaker en telkens ontstaat er iets bijzonders. Ik verheug me op nog zoveel moois samen, "la vita e bella, le notte sono dolce." You've got rhythm my friend!

F.A.M. Brooymans, beste Frans, toeval bestaat niet. Jij beheerst een palet aan competenties waarmee visie en betrokkenheid floreren. Na vele jaren van klinische alertheid heb jij een vertaalslag gemaakt van buigen en strekken waar heel veel patiënten dankbaar mee weglopen. "Pain is inevitable, suffering is optional." Dank je wel voor je stimulans en onvergetelijk cadeau.

René Elsbeek, cher rrené, onze ontmoeting 9 jaar geleden heeft geleid tot wederzijdse waardering en respect. Als het proefschrift de bekroning is op mijn wetenschappelijk werk, dan zijn onze gesprekken de apotheose van een bijzondere vriendschap. Merci mon ami.

Charles H. Brown Jr. MD, dear Charlie, your teaching is truelly inspirational. I feel very priviliged to be able to be part of our mutual knee courses and to share our passion for education & jazz. Thank you for your dear friendship and I hope to welcome you for the years to come at our annual Utrecht course. Next stop, North Sea Jazz Festival 2016!

Chris van de Vijfeijke, wij delen een passie voor drums en onderwijs. Jouw inspirerende drumlessen verleggen mijn muzikale grenzen. Dank voor je enthousiasme, op maat gesneden inzicht in fusion & jazz en je 'stoeltje' bij Access Denied. Een proefschrift is eindig, maar ik hoop dat wij onze passie voor muziek nog lang samen mogen delen.

Dave Weckl, dear Dave, thank you very much for your musical experience and inspiration. I enjoy your orthopaedic view on playing drums. Balance is essential for optimal performance. Your personal lessons, masterclasses and the once in a lifetime oppurtunity for me to play with the dream band featuring James Genus, Vinny Valentino, Stu Mindeman and Chrissi Poland at the DrumFantasyCamp 2015 in Chicago are moments to cherish forever.

Dr.ir. K.B.M. Peters, lieve Karin, goed voorbeeld doet volgen. Discussie is eeuwig en ik hoop dat het publiek net zoveel zal begrijpen van mijn promotie als dat ik van jouw verdediging heb genoten.

Muzikale vrienden van Access Denied, Digedig & One-Shot Wonder: Anton, Mon, Mat, Elke, Lilian, ID, Theo, Roel, Ernst-Jan, Abigail, Harm-Jan, Ruud, Anton en Henco, jullie zorgen voor de ruimte in mijn hoofd en mijn allergrootste glimlach!

Vrienden, mes amis, my friends:
"Don't walk behind me, I may not lead.
Don't walk in front of me, I may not follow.
Just walk beside me and be my friend" - Albert Camus
Dank voor jullie vriendschap, op naar het feest!

Mijn lieve schoonouders: Ans en Jack, altijd een luisterend oor, oprechte interesse en nieuwsgierig naar wat mij bezig houdt. Dank jullie wel, ook voor jullie geweldige dochter.

Mijn liefste ouders: Annemie en Martin, jullie beroemde uitdrukking "net dat beetje meer" staat symbool voor al mijn belevenissen. Merci énormément voor jullie dierbare opvoeding, bereidheid tot internationale avonturen en de waarden van een hecht gezinsleven. Jullie wijze levenslessen zijn zo waar gebleken. Ik ben trots op jullie joie de vivre in Frankrijk en vind het fantastisch dat we ook dit samen mogen beleven. "La nourriture est la base de la vie" & "Tè, maak er nog een open, het is gezellig."
Je vous aime infiniment!

Mijn meest dierbaren: Patricia, Bas, Daan en Gijs.
Terugkerende uitspraken in Huize Janssen in de afgelopen jaren: "papa zit weer achter de computer" en "geeft niks als het wat langer duurt pap, als we uitgegroeid zijn heeft mama ons een mooi pak beloofd voor jouw promotie." Lieve Bas, Daan en Gijs, het wachten wordt beloond ☺ Ik ben zo trots op jullie!

Liefste Patricia, opschrijven wat jij allemaal voor de jongens en mij betekent zou een heel boek kunnen vullen. Jouw onvoorwaardelijke steun en liefde hebben mijn carrière en proefschrift glans gegeven. Je warmte, organiserend talent, kracht om mensen te motiveren en spontaniteit geven jou kleur en grote waardering thuis, in je flitsende GGzE carrière en je bestuursfuncties bij de KNLTB en raden van toezicht. Jij bent de altijd lopende motor achter ons gezin, houdt mij met twee benen op de grond als mijn enthousiasme de realiteitszin weer eens overstijgt maar biedt altijd ruimte voor ontdekking en plezier. Ik ben supertrots op je. "Leuk is voor thuis" en wat is het thuis geweldig! Merci énormément, ik hou zielsveel van je!

De datum is er, het is.

"If someone offers you an amazing opportunity and you're not sure you can do it, say yes – then learn how to do it later."
(Richard Branson)

Curriculum Vitae

Rob P.A. Janssen was born on April 19, 1968 in Heerlen (The Netherlands). He graduated from high school in 1986 (International Baccalaureate; International School Manila, Philippines) and studied medicine at Université de Caen (France), Maastricht University (The Netherlands) and Brown University (Providence RI, USA). He attended the general surgery and orthopaedic surgery residency programmes at Sint Maartens Gasthuis Venlo, Maastricht University Medical Centre and Máxima Medical Centre Veldhoven (1996-2002, The Netherlands).
In 2002, he joined the current Coöperatie Orthopedie Groot Eindhoven, an association of 15 orthopaedic surgeons in the greater Eindhoven area (The Netherlands). His specialised knee practice is located at the Orthopaedic Centre Máxima Eindhoven, a tertiary referral centre for sports medicine and multiligament-injured knees in The Netherlands.
Besides his orthopaedic practice, he is fond of scientific research and education. Since 2008, he is deputy director of the orthopaedic residency programme at Máxima Medical Centre, Eindhoven-Veldhoven. From 2011-2014, he has enjoyed his presidency of the Dutch Arthroscopy Society (Nederlandse Vereniging voor Arthoscopie - NVA). He currently holds positions on various review boards and is lecturer on topics of knee, trauma and sports medicine. He is faculty and member of the organizing committee at annual (post)masters programmes and international advanced knee courses. He is also partner in the Sports Clinical Expertise Centre and member of the board of directors of scientific and medical organisations.

Work is interesting and life is fun spending time with family & friends and playing soul, fusion and jazz music in 2 bands. He is happily married to Patricia and they have 3 sons: Bas, Daan and Gijs.

Full biography @ www.rpajanssen.com

"Eventually all things fall into place. Until then, laugh at the confusion, live for the moments, and know everything happens for a reason."
(Albert Schweitzer)

Dit boek is oprecht een co-creatie van een wonderlijk geïnspireerd drietal Rob Janssen, Tayfun van Zantvoort en Rhea Strik in de personages van: *arts-promovendus, ontwerper* en *kunstenaar*. Ieder van hen droeg op een unieke wijze bij aan de totstandkoming van het proefschrift.

De *promovendus* bracht op een zomeravond *de ontwerper* en *de kunstenaar*, volkomen vreemden van elkaar, bijeen: een mengeling van lef, vertrouwen en fijnzinnige intuitie of was het visionair? Het werd een 'latertje', ... en er was een moment dat het scheen alsof we elkaar al eeuwen... het fundament was gelegd. Vervolgens luidde de opdracht: "*Het levenswerk moest wel terdege de uitstraling hebben van een proefschrift, maar een creatieve, kunstzinnige 'touch' werd onmiddellijk en met verve omarmd.*" Dit was niet tegen dovemansoren gezegd. Spelenderwijs werd het standaardformaat losgelaten en kreeg het boek een eigenzinnig karakter.. de toon was gezet. De ruimhartige *promovendus* "*kon het wel waarderen*" (een veel gehoorde R.J. uitspraak). Bij het zien van *de eerste out of the box* concepten hield zijn altijd brede lach gelijke tred met de gepassioneerde aanpak van *de ontwerper*, het viel in goede aarde. Het proces van scheppen en herscheppen, passen en meten, wikken en wegen, stoeien en vervloeien, *till the very end* was inmiddels een feit.

Rob: terug naar dat ene moment; ik werd er stil van toen je vroeg: "*zou het werk Gracias op de omslag van mijn proefschrift kunnen staan?*" Jouw levenswerk enerzijds en mijn meest krachtige werk anderzijds samen te brengen, klonk als muziek in mijn oren. Zo vervullend, passend en tegelijkertijd buitengewoon eervol. "*Gracias*", en je wijst een plek aan op het kunstwerk: "*daar zit ie, elke dag zie ik 't de knie..*" was dus ook de verbinding met je werk. Ja het is waar, dit uitermate vernuftig, meest complexe gewricht van het menselijke lichaam heeft al jaar en dag jouw aandacht en fascinatie; grondig bestudeerd, eindeloos tot in de fijnste cel)-structuren aanschouwd terwijl je je ontwikkelde tot een meer dan bekwaam chirurg, die *helemaal* begrepen heeft, hoe nauw het luistert aan de '*articulus genus*' met zijn anatomische perfectie te opereren.

Tayfun: het is inderdaad spannend om eigen werk uit handen te geven. En wat een geruststelling dat de essentie "gevat werd" en je respectvol daarmee omging. Een geschenk om met jou een open minded geest op reis te gaan. Niets is vanzelfsprekend.. daarom was ik aangenaam verrast dat Gracias voor jou een bron van inspiratie was. Oprecht en bevlogen gaf je zeer vanuit je gevoel uitdrukking aan datgene wat je *nu* weer ontdekt had.. Het is zozeer in de vormgeving en sfeer van het boek terug te vinden. Gracias reist als een rode draad in verschillende gedaantes er door heen... in delen en gehelen met steeds weer andere interventies. De ene keer ondeugend, dan weer fier of stevig te verschijnen of te verdwijnen. Mooie positionering en een fraaie balans tussen 'niets' en 'iets'. Een uitnodiging tot verder lezen: *gracias*... Voor jou deze laatste woorden:

"*Scheppen is niet alleen dat wat je zichtbaar maakt en waarneemt. Het is zeker ook datgene wat je niet ziet en door het werk heen komt. Indien het beeld omgeven wordt door een zekere ruimte en die ene spanning heeft, is er sprake van fusion en dat is hier gebeurd.*"

Rhea Strik - Visual Art - www.rheastrik.nl

Over het maken van dit boek vanuit mijn perspectief.

Mijn naam is Tayfun van Zantvoort en ik ben de hoofddesigner en eigenaar van het bedrijf MonTay Media.

Toen Rob me vroeg om mee te denken over het ontwerp van zijn proefschrift, had ik nooit gedroomd waar de facetten van deze reis mij zouden brengen en hoe het mij zou beïnvloeden als persoon. Het combineren van het sublieme kunstwerk van Rhea Strik met haar meesterwerk 'Gracias' en het wetenschappelijk levenswerk van Rob heeft een samensmelting van drie totaal verschillende visies tot stand gebracht. Al deze visies hebben ieder zo veel lagen aan levenservaring en al dat het met zich meebrengt. Hoe deze samenwerking er uit zou zien, horen en voelen, was een vraag die we niet eerder hadden kunnen beantwoorden.

Nu na vele sessies praten, dineren en vergaderen, hebben we de passies van elkaar ontdekt, visies van het leven en misschien nieuwe delen van onszelf beleefd waarvan we niet wisten dat die er waren. Een geweldige reis die ik niet gemist zou willen hebben. Veel dank aan Rob en Rhea voor deze levenslessen die niet veel mensen zullen ervaren in hun leven. Ik voel me verrijkt.

T. van Zantvoort, MonTay Media, www.montay.nl


20
RPA
PhD
16