SUBJECTIVE AND OBJECTIVE ASSESSMENT OF PHYSICALLY ACTIVE PEOPLE WITH KNEE INJURY

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by

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"*O meu Obrigado a...*"

This thesis is the end-result of more than 3 years of my life, with up and down moments, of adventure, happiness and some sadness, of reason but a lot of heart too, of dreams, hopes and expectations, of illusion and frustration, of "*saudade*", friendship, passion and love...

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TABLE OF CONTENTS

List of Figures **VII**
List of Tables **VIII**
List of Abbreviations **IX**
List of Publications **XII**
Summary of the Thesis **XIII**

GENERAL INTRODUCTION

1. Knee Anatomy and Biomechanics **15**
1.1. Anatomical Overview **15**
1.1.1. Tibiofemoral Joint **16**
1.1.2. Patellofemoral Joint **17**
1.2. Biomechanical Overview **18**
2. Knee Injuries in Active Individuals **19**
2.1. Defining Concepts **19**
2.1.1. Knee Injury **19**
2.1.2. Physically Active **20**
2.2. Epidemiology **20**
2.2.1. Physical Activity and Sport **21**
2.2.1.1 Traumatic Knee Injuries **21**
2.2.1.2 Overuse Knee Injuries **22**
2.2.2. Gender Factor **23**
2.2.3. Age Factor **24**
3. Assessment Outcomes Following Knee Injury **25**
3.1. Patient-Reported Outcome Measures **25**
3.1.1. General Health Instruments **26**
3.1.1.1. SF-36 **27**
3.1.1.2. EQ-5D **27**
3.1.2. Knee Specific Instruments **28**
3.1.2.1. Lysholm Knee Scale **28**
3.1.2.2. WOMAC **29**

3.1.2.3. KOOS **29**
3.1.2.4. IKDC Subjective Form **30**
3.1.2.5. Modified Cincinnati Knee Score **30**
3.1.3. Physical Activity Instruments **31**
3.1.3.1. Tegner Activity Scale **32**
3.1.3.2. Marx Activity Rating Scale **32**
3.1.3.3. Modified Baecke Questionnaire **33**
3.2. Objective Clinical Outcome Measures **33**
3.2.1. Cardiorespiratory Deconditioning **34**
3.2.2. Cardiorespiratory Fitness Testing **36**
3.2.2.1. Single-Leg Cycling **37**
3.2.2.2. Counterweighted Single-Leg Cycling **38**
3.2.2.3. Self-Paced Protocols **39**
3.3. Psychometric Properties **41**
3.3.1. Reliability **41**
3.3.1.1. Internal Consistency **42**
3.3.1.2. Test-Retest Reliability **42**
3.3.2. Validity **43**
3.3.2.1. Content Validity **43**
3.3.2.2. Criterion Validity **43**
3.3.2.3. Construct Validity **44**
3.3.3. Responsiveness **44**
4. Literature Review Summary **45**
5. Aims and Outline of the Thesis **46**

PART I - PATIENT-REPORTED MEASURES OF KNEE FUNCTION AND SPORT PARTICIPATION

CHAPTER 1: Measuring Physical Activity and Sports Participation Following Autologous Cartilage Implantation: A Systematic Review

1. Abstract **49**
2. Context **50**
3. Objectives **51**
4. Evidence Acquisition **51**
5. Evidence Synthesis **56**
6. Discussion **67**
7. Conclusion **70**

CHAPTER 2: Normative Values for the KOOS in Recreational Male Marathon Runners. Stratified by Age Group and Knee Running-Related Injuries

1. Abstract **72**

2. Introduction **73**

3. Methods **74**

4. Results **77**

5. Discussion **87**

6. Conclusion **90**

PART II - SINGLE-LEG CYCLING EXERCISE TESTING

CHAPTER 1: Reliability of Self-Paced Single-Leg Cycling Exercise Testing

1. Abstract **93**

2. Introduction **94**

3. Methods **95**

4. Results **99**

5. Discussion **105**

6. Conclusion **107**

CHAPTER 2: Validity of Self-Paced Single-Leg Cycling Exercise Testing

1. Abstract **109**

2. Introduction **110**

3. Methods **111**

4. Results **115**

5. Discussion **118**

6. Conclusion **120**

CHAPTER 3: Cardiovascular Responses to Maximal Single-Leg Cycling: The Effect of the Counterweight

1. Abstract **122**

2. Introduction **123**

3. Methods **124**

4. Results **128**

5. Discussion **133**

6. Conclusion **136**

GENERAL DISCUSSION

1. Overall Summary **137**

2. Conclusion and Perspectives **143**

References **144**

Appendices **185**

LIST OF FIGURES

Figure 1	Anterior and posterior views of the right knee joint complex showing the articular capsule and the external ligaments	**16**
Figure 2	Cardiac morphological and physiological changes associated with detraining	**36**
Figure 3	97 N counterweight device attached to the non-exercising arm crank	**39**
Figure 4	Rate of perceived exertion 6-20 Borg Scale	**40**
Figure 5	Flow diagram on reporting the selection process of studies	**57**
Figure 6	Marathon runners selection flowchart	**78**
Figure 7	Pairwise differences between single-leg cycling self-paced tests	**101**
Figure 8	Raw data Bland and Altman's plots between sessions	**102**
Figure 9	Power output and cadence profiles throughout the single-leg cycling self-paced tests	**103**
Figure 10	Oxygen uptake profile throughout the single-leg cycling self-paced tests	**104**
Figure 11	Power output and oxygen uptake profiles throughout both single-leg cycling exercise testing protocols	**117**
Figure 12	The effect of the counterweight on oxygen uptake profile during single-leg cycling maximal testing	**131**
Figure 13	The effect of the counterweight on power output and cadence profiles during single-leg cycling self-paced testing	**132**

LIST OF TABLES

Table 1	Evidence Levels from the Oxford Centre for Evidence-based Medicine	**53**
Table 2	Surgical and demographic overview of included studies	**59**
Table 3	Summary of patient-reported instruments used in each study	**62**
Table 4	Characteristics of the patient-reported instruments	**66**
Table 5	Description of participants stratified by history of knee running-related injuries	**79**
Table 6	KOOS outcomes stratified by age group and history of knee running related injury	**80**
Table 7	Comparison of KOOS outcomes between age groups of runners without knee injury	**83**
Table 8	Comparison of KOOS outcomes in the current study with previously published comparable normative values for a non-injured male population in 18-34 years old age group	**85**
Table 9	Comparison of KOOS outcomes in the current study with previously published comparable normative values for a non-injured male population in 35-54 and 55-74 years old age groups	**86**
Table 10	Individual peak power output and peak oxygen uptake data	**100**
Table 11	Differences between sessions and inter-session reliability	**100**
Table 12	Single-leg cycling self-paced *vs.* graded exercise testing	**116**
Table 13	Interactions and main effects of protocol and counterweight setting on power output, physiological and perceptual responses to single-leg cycling tests	**129**

LIST OF ABREVIATIONS

ACSM	American College of Sports Medicine
ACI	autologous cartilage implantation
ACL	anterior cruciate ligament
ADL	activities of daily living
ARS	activity rating scale
$BL_{1\text{-}min}$	1-min post-test blood lactate
BMI	body mass index
CACI	collagen autologous chondrocyte implantation
CAIS	Cartilage Autograft Implantation System®
CCI	Characterized Chondrocyte Implantation®
CDR	clinical data repository
CI	confidence interval
CINAHL	Cumulative Index for Nursing and Allied Health Literature
CKS	Cincinnati Knee Score
CV	coefficient of variation
CW0	no counterweight
CW10	10 kg counterweight
EQ-VAS	EuroQol visual analogue scale
FDA	Food and Drug Administration
GXT	graded exercise test
GXT_{CW0}	graded exercise test without counterweight
GXT_{CW10}	graded exercise test with a 10 kg counterweight
HR	heart rate
HR_{peak}	peak heart rate
ICC	intraclass correlation coefficient
IQR	interquartile range
IKDC	International Knee Documentation Committee
KOOS	Knee Injury and Osteoarthritis Outcome Score

LOA	limit of agreement ratio
MACI	Matrix-induced Autologous Chondrocyte Implantation®
MDC	minimal detectable change
MF	microfracture
OA	osteoarthritis
OAT	osteochondral autograft transplantation
$Pain_{peak}$	peak pain
PACI	periosteal cover Autologous Chondrocyte Implantation
PEdro	Physiotherapy Evidence Database
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PPO	peak power output
PRO	patient reported outcome
QOL	quality of life
RB	rehabilitation
RCTs	Randomized controlled trials
RER	respiratory exchange ratio
RER_{peak}	peak respiratory exchange ratio
RPE	rate of perceived exertion
RPE_{peak}	peak rate of perceived exertion
RRI	running-related injuries
SEM	standard error of measurement
SF-36	Medical Outcomes Study 36-Item Short Form
S1	session 1
S2	session 2
S3	session 3
SD	standard deviation
SEm	standard error of measurement
SLC	single-leg cycling
SPT	self-paced test
SPT_{CW0}	self-paced test without counterweight
SPT_{CW10}	self-paced test with a 10kg counterweight
SR	systematic review
TAS	Tegner Activity Scale
UK	United Kingdom
US	United States

VE	minute ventilation
VE_{peak}	peak minute ventilation
VO_2	oxygen uptake
VO_{2max}	maximal oxygen uptake
VO_{2peak}	peak oxygen uptake
WB	weight bearing
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

LIST OF PUBLICATIONS

Articles published in peer reviewed journals:

Santos-Magalhaes, A. F., & Hambly, K. (2014). Measuring physical activity and sports participation after autologous cartilage implantation: a systematic review. *J Sport Rehabil*, *23*(3), 171-181.

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SUMMARY OF THE THESIS

This thesis was supervised by Dr. Karen Hambly (University of Kent, UK) and co-supervised by Prof. Samuele Marcora (University of Kent, UK)

Knee injuries are highly prevalent in physically active individuals and are frequently associated with sport participation. Independently of the nature of the injury, subjective and objective clinical measures are used to assess, monitor and evaluate treatment outcomes in this population. To be clinically meaningful, these outcome measures should be relevant to the condition, the anatomical area, the individual or population, and importantly, possess adequate psychometric properties.

Despite a high prevalence of knee injuries, there are several aspects of the subjective and objective knee evaluation in physically active individuals that remain unclear or have not been considered in previous research.

The main aim of the present thesis was to fill some of the gaps identified in the literature regarding both subjective and objective knee measures in physically active individuals. Therefore, this thesis was divided into two distinct parts. The first part looked at the patient-reported outcome (PRO) measures of the knee and physical activity, and consisted of two studies. The first study was a systematic review conducted to explore the PRO measures that are commonly used in the evaluation of physical activity and return to sport following autologous chondrocyte implantation (ACI). Aiming as well, to provide a critical analysis of these instruments from a rehabilitative perspective. This review revealed not only the heterogeneity in the selection, but also in the timing and reporting of patient-reported activity scoring instruments following ACI, which makes a systematic comparison difficult and introduces bias into the interpretation of these outcomes. Another important finding of this review, was that the instruments currently used to evaluate postoperative outcomes in an articular cartilage repair population do not always fulfil the rehabilitative needs of physically active individuals. The second study was conducted in recreational marathon runners and aimed to provide normative values for a widely used knee specific PRO measure in athletes with knee injury, the Knee Injury Osteoarthritis Outcome Score (KOOS). Alongside the normative KOOS subscales values stratified by age group and history of

knee injury that were presented, this study also showed that recent history of knee running-related injury (RRI) has a negative impact on the KOOS scores. In runners with no history of knee RRI, the results observed suggested a lack of interaction between KOOS subscale values and age. Furthermore, the KOOS values seen were substantially higher compared to previously published normative population-based KOOS values.

The second part of the present thesis comprised three experimental studies concerning single-leg cycling (SLC) exercise testing, in particular assessing the potential use of the self-paced test (SPT) concept as an objective measure following knee surgery. The first study analysed the reliability of a 5x2 min stages SPT anchored to the rate of perceived exertion (RPE) for SLC exercise testing. This study showed that this test protocol elicits reliable cardiorespiratory and metabolic responses. The second study examined the validity of the SPT protocol used in the previous study, through a concurrent comparison against a conventional fixed power incremental SLC exercise test. This investigation showed that the 5x2 min SPT provides a valid objective means for assessing peak aerobic capacity in SLC exercise testing. Moreover, it may be associated with increased activity enjoyment comparatively to conventional testing. The third and last experimental study investigated the effect of a 10 kg counterweight device (CW10) on cardiorespiratory, metabolic and perceptual responses to SLC exercise testing. The results of this study demonstrated that the CW10 despite eliciting an improvement in the activity enjoyment, did not affect peak cardiorespiratory and metabolic responses to SLC exercise testing. When matched for test duration the SPT elicited higher peak power output and peak oxygen consumption than conventional incremental testing, regardless of the CW10 usage or not.

In conclusion, the original work of the present thesis increases the body of knowledge of two distinct, but complementary fields in the subjective and objective knee assessment of physically active individuals. The outcomes provided both on PRO measures and SLC exercise testing, may have impact on the clinical practice of clinicians, sport rehabilitation professionals and researchers.

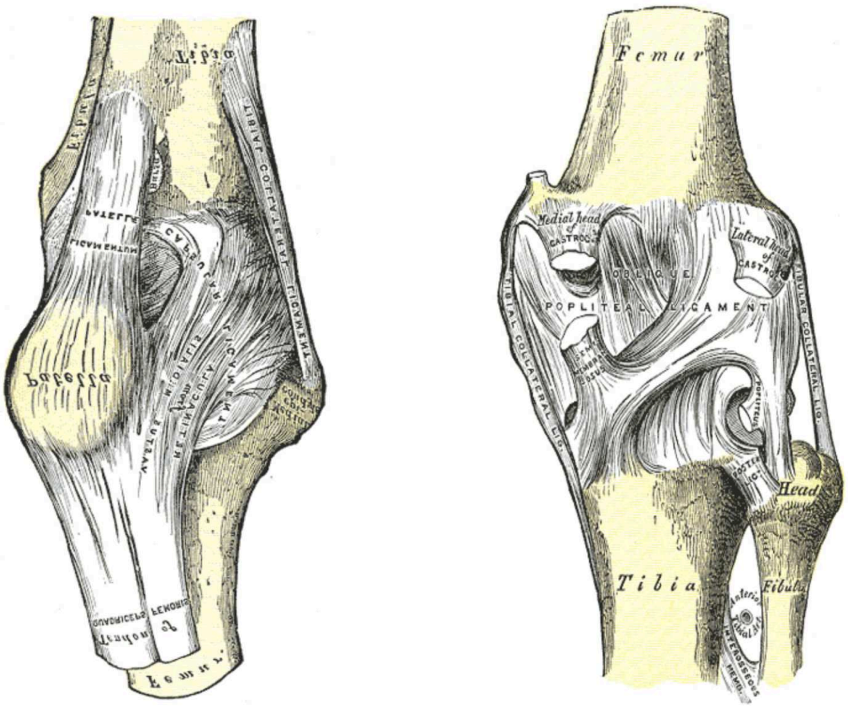
GENERAL INTRODUCTION

1. Knee Anatomy and Biomechanics

It is well established that anatomy follows function. The knee joint is not only the largest, but also one of the most intricate joints in the human body. Understanding the injured knee depends on a fundamental knowledge of the anatomy and biomechanical function of the structures that comprise the knee (Goldblatt & Richmond, 2003; Standring, 2015).

1.1. Anatomical Overview

The knee joint complex consists of the tibiofemoral and the patellofemoral synovial joints (Standring, 2015). Although, the proximal tibiofibular joint may also be considered part of the knee complex (Hirschmann & Muller, 2015). Typically, synovial joints are characterised by a layer of hyaline cartilage covering the articular surfaces of bones, within a joint cavity that contains a viscous synovial fluid, lined with synovial membrane and reinforced by a fibrous capsule and ligaments (Standring, 2015).



Anterior view Posterior view

Figure 1- Anterior and posterior views of the right knee joint complex showing the articular capsule and the external ligaments

The images are from the Gray's Anatomy of the Human Body book (Gray, 1918) which has been transferred into the public domain

1.1.1. Tibiofemoral joint

The distal end of the femur bone expansions forms the convex lateral and medial condyles. Both lateral and medial femoral condyles articulate with the proximal end of the tibia, the tibial plateau, forming the tibiofemoral joint. The knee structures can either be intracapsular or extracapsular. Enclosed inside the joint capsule there are two cruciate ligaments, as well the medial and lateral meniscus (Standring, 2015). The cruciate ligaments are named anterior and posterior in reference to their tibial attachment; their main function is to maintain the anterior and posterior stability of the knee, respectively, alongside with rotational stability (Rong & Wang, 1987). The

menisci consist of two semilunar, intracapsular, fibrocartilaginous laminae that widen and deepen the tibial articular surfaces, increasing the congruency of the joint and acting as a mechanical cushion. The medial meniscus is larger and “c” shaped, while the lateral meniscus is smaller and “o” shaped; they connect anteriorly via the transverse ligament (Standring, 2015). Laying extracapsularly, on either side of the tibiofemoral joint, are the medial collateral ligament and the lateral collateral ligaments. The collateral ligaments work to stabilise and translate forces medially and laterally, providing sideways stability to the knee (Dwyer & Whelan, 2012).

1.1.2. Patellofemoral Joint

On the anterior surface of the distal femur, the two condyles form a hollowed groove, or trochlea, that articulates with the patella. The trochlea is divided into medial and lateral facets. In most people, the lateral trochlear notch extends more proximally, is larger overall, and projects further anteriorly than the medial facet (Standring, 2015). The patella is a large flat, triangular sesamoid bone located anterior to the knee joint. It is situated within the tendon of the quadriceps femoris muscle and provides a central point of attachment for the quadriceps tendon and patellar ligament (Fox, Wanivenhaus, & Rodeo, 2012). With the knee extended, the patella is mobile in a medial-lateral direction because it is not engaged in the trochlear groove. During knee flexion, the stability of the patella in the trochlear groove is achieved by a combination of articular geometry, static and muscular restrain (Goldblatt & Richmond 2003). The lateral facet of the trochlea provides a buttress to lateral patellar displacement. The static restraints are provided by the patellofemoral and patellotibial ligaments, which limit both lateral and medial patellar dislocations (Fox, Wanivenhaus, & Rodeo, 2012). The vastus medialis obliquus component of the quadriceps muscle tension contributes to the articular alignment by pulling the patella not only proximally and medially but also posteriorly (Feller et al., 2007).

1.2. Biomechanical Overview

In various recreational and sport activities, both patellofemoral and tibiofemoral joints are exposed to large forces while accommodating the considerable knee joint mobility (Mesfar & Shirazi-Adl, 2005). The primary motion of the knee is flexion-extension; however, it has some freedom in rotatory movements. Knee motion is normally defined as starting from 0 degrees (the neutral position), when the tibia and femur are in line in the sagittal plane. Active knee hyperextension allows up to 5 degrees and knee flexion leads to approximately 130 degrees. Often in physically active individuals, the active motion is limited by apposition of the posterior thigh and calf muscle masses. As seen in normal gait, terminal flexion and extension are accompanied by tibial internal and external rotation, respectively (Standring, 2015). The patella is part of the extensor mechanism of the knee, along with the quadriceps femoris muscle, quadriceps tendon and patellar tendon. It works as a complex lever that magnifies the moment arm of the extensor mechanism, increasing the mechanical advantage of the extensor muscles (Grelsamer & Weinstein, 2001). This increased moment arm reduces the quadriceps force required to extend the knee by 15 % to 30 % (Goldblatt & Richmond, 2003). Primary muscles of knee control include the quadriceps anteriorly, the hamstrings and gastrocnemius posteriorly, the gluteus medius and tensor fascia lata laterally, and the adductors medially (Dugan, 2005). These muscles regulate forces in the lower extremity and decelerate the body over the lower limb during activities as running, landing from jumping, cutting, and stopping (Richards & Kibler, 1998).

2. Knee Injuries in Physically Active Individuals

2.1. Defining Concepts

2.1.1. Knee Injury

A theoretical definition of an injury is complicated due to a lack of basic scientific distinction between disease and injury (Langley & Brenner, 2004). An injury occurs when a body tissue is exposed to stress in amounts that exceeds its threshold of acute or chronically physiological tolerance (McBain et al., 2012). Knee injuries are typically framed within the musculoskeletal injuries category. Musculoskeletal injuries are collectively referred to as injuries that involve one or a combination of structures, including bones, muscles, tendons, ligaments and associated connective tissues (Delforge, 2002). Knee injuries are classified according to the affected structure or structures, its severity and by the injury mechanism (Bollen, 2000; Hayes, Brigido, Famadar, & Propeck, 2000). The need for knee surgery is often seen as a measure of injury severity, but it can also be an indication of the economic costs of knee injuries (Louw, Manilall, & Grimmer, 2008). Although, in competitive sport, the injury severity is mainly measured by the time lost from competition and practice (Fuller et al., 2006; Fuller et al., 2007). Similar to other anatomic regions, knee injuries can be divided into acute or traumatic and overuse injuries (Hauret, Jones, Bullock, Canham-Chervak, & Canada, 2010). A consensus statement for soccer has outlined a traumatic injury as an injury resulting from a specific, identifiable event that requires any treatment by a physician. On the contrary, overuse injuries are associated with repeated micro-traumas, without a single, identifiable event responsible for the injury (Fuller et al., 2006). These repetitive micro-traumas to normal tissues can cause overuse injuries if the tissues are not given adequate time to heal and repair damage (Cuff, Loud, & O'Riordan, 2010). Terms such as gradual onset and low intensity forces of long duration have also been used in the characterization of an overuse injury (Bahr, 2009; Knight, 2008).

2.1.2. Physically Active

Physical activity is classically defined as “any bodily movement produced by skeletal muscles that results in energy expenditure above the basal level” and exercise is described as a sub set of physical activity that is “planned, structured and repetitive and has a final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen, Powell, & Christenson, 1985, p. 126). Recognition of the health and functional hazards of a sedentary way of life has led numerous health authorities worldwide to promulgate public health recommendations for physical activity (Blair, LaMonte, & Nichman, 2004). Conventionally, individuals who meet the minimum physical activity recommendations are characterized as being physically active. The current physical activity recommendations, including the United Kingdom (UK) guidelines, emphasize that adults aged 18–64 should remain physically active by engaging in a minimum of 150 min of moderate-intensity aerobic exercise per week, or do at least 75 min of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity (Bull et al., 2010; Garber et al., 2011; Tremblay et al., 2011; World Health Organization, 2010). The American College of Sports Medicine (ACSM) 2011 guidelines also highlight that adults should perform resistance exercises, flexibility exercises and neuromotor exercises 2-3 days per week (Garber et al., 2011).

2.2. Epidemiology

Knee injuries are one of the highest clinical and public health injury-related burdens. In the United States (US), an estimated 6,664,324 knee injuries presented to emergency departments between 1999 and 2008, which represents a rate of 2.29 knee injuries per 1000 habitants (Gage, McIIvain, Collins, Fields, & Comstock, 2012). A study conducted in an accident and emergency department in the UK, covering a population of 460,000 habitants, has shown an even higher incidence rate, above 5.5 knee injuries per 1000 habitants (Chandratreya, Spalding, & Correa, 2006). Due to the

frequent need for surgical repair and long-term rehabilitation (Gage et al., 2012), knee injuries pose substantial costs for the health systems (Loes, Dahlstedt, & Thomée, 2000). Moreover, these injuries may result in the early development of knee osteoarthritis (OA) (Muthuri, McWilliams, Doherty, & Zhang, 2011) and permanent disability to sport and work (Bollen, 2000). The physical activity and sport participation profile, as well as gender and age, have been shown to be important determinants of the rate and pattern of knee injuries (Gage et al., 2012).

2.2.1. Physical Activity and Sport

The overall incidence of knee injuries is highly related to the physical activity profile of the population. It has been estimated that 20–25% of all knee injuries occur while performing sports (Maes, Andrianne, & Remy, 2002). Compared to sedentary individuals, sport participants tend to have a higher proportion of all-cause and activity-related musculoskeletal injuries, including knee injuries (Hootman et al., 2001). Knee injuries in particular, may lead to a substantial reduction in physical activity, prolonged rehabilitation periods and sport participation absence. Importantly, the type of sport engaged in has been shown to be linked with the nature and injury mechanism (Kujala et al., 1995; Majewski, Susanne & Klaus, 2006; Ristolainen et al., 2010).

2.2.1.1. Traumatic Knee Injuries

Team and contact sports like soccer, handball, ice-hockey and basketball, and individual sports such as skiing and alpinism are considered high risk sports for traumatic knee injuries (Loes et al., 2000). From these, alpine ski and soccer present the highest incidence rate of knee injuries (Kujala et al., 1995; Majewski et al., 2006). Knee ligaments sprains are the most common injuries in Alpine skiers, accounting for approximately 30% of all injuries (Stenroos & Handolin, 2014; Warme et al., 1995). The medial collateral ligament and the anterior cruciate ligament (ACL) are the most

affected ligaments (Warme, Feagin, King, Lambert, & Cunningham, 1995). In soccer, an early review of six major epidemiological studies has shown that knee injuries consistently represent 12-20 % of the total injuries (Keller, Noyes, & Buncher, 1987). This incidence rate compares well with more recent studies (Ekstrand, Hagglund & Walden, 2011; Peterson, Junge, Chomiak, Graf-Baumann, & Dvorak, 2000). The most frequent knee injuries in soccer are contusions, medial meniscus injuries, collateral ligaments and ACL injuries (Quisquater et al., 2013). In soccer, like in other team sports, traumatic knee injuries are more likely to occur during competitive activities rather than during training sessions (Ekstrand, Hagglung, & Walden, 2011; Hawkins & Fuller, 1999; Quisquater et al., 2013).

2.2.1.2. Overuse Knee Injuries

In endurance sports such as long-distance running and triathlon, overuse injuries affecting the knee are substantially more prevalent than traumatic injuries (Ristolainen et al., 2010; Andersen, Clarsen, Johansen, & Engebretsen, 2013). In marathon runners, several studies have shown incidence rates of knee injuries ranging between 5 and 32 % (Chang, Shih, & Chen, 2012; Kretsch et al., 1983; Maughan & Miller, 1993; Van Middelkoop, Kolkman, Van Ochten, Bierma-Zeinstra, & Koes, 2008a, 2008b). This incidence rate variability might be explained by the methodological differences between studies, particularly, in the definition of injury and in the injury recall period considered. Overuse injuries may affect team sports as well, especially at an elite level (Augustsson, Augustsson, Thomee, & Svantesson, 2006; Stubbe et al., 2015) and among young athletes, when the training and competition loads increase rapidly (Visnes & Bahr, 2013).

Amongst the most common and limitative overuse injuries related to the knee are patellofemoral pain syndrome, patellar tendinopathy and iliotibial band friction syndrome (Galloway, 2013; O'Keeffe, Hogan, Eustace, & Kavanagh, 2009). Patellofemoral pain syndrome is characterized by anterior knee pain and underlying multifactorial causes. These causes include tendinopathies of the knee extensor apparatus, patellar instability and cartilage injuries (Petersen et al., 2014). A study conducted in runners, has shown that the patellofemoral pain syndrome may account for

nearly 25 % of all knee injuries (Taunton et al., 2002). The patellar tendinopathy, also known as jumper's knee, is a syndrome associated with micro tears and collagen degeneration in the patellar tendon without inflammatory cells being present (Hamilton & Purdam, 2004), that results in pain and functional impairment (Visnes & Bahr, 2007). It is more prevalent in sports that require high demands on speed and power for the leg extensors, e.g. volleyball and basketball (Lian, Engebretsen & Bahr, 2005). The iliotibial band friction syndrome is a common inflammatory injury of the lateral aspect of the knee, particularly in runners, cyclists and other endurance sports (Taunton et al., 2002; Holmes, Pruitt, & Whalen, 1993). It is typically caused by friction/rubbing of the distal portion of the iliotibial band over the lateral femoral condyle with repeated flexion and extension of the knee (Ellis, Hing & Reid, 2007).

2.2.2. Gender Factor

In addition to the type of sport performed, gender is also an important determinant for the frequency of knee injury (Majewski et al., 2005). There is a strong level of evidence suggesting a higher injury vulnerability of the knee in females for both traumatic and overuse injuries. Although, studies have been conducted primarily in young athletic populations (Arendt & Dick, 1995; Hutchinson & Ireland, 1995; Louw et al., 2008; Majewski et al., 2005). Sporting females are particularly at higher risk than their male counterparts for ACL and patellofemoral pain syndrome (Dugan, 2005). Anterior cruciate ligament injury risk in female athletes has been shown to be three to eight times greater than in similarly trained male athletes (Smith et al., 2012). The main intrinsic causes for this higher risk are the narrower femoral notch (Ireland, Ballantyne, Little, & McClay, 2001), increased ligament laxity, and decreased joint stiffness in external tibial rotation (Park, Wilson, & Zhang, 2008). The increased ligament laxity and decreased joint stiffness have been associated with the menstrual cycle and the hormonal status (Arendt, Bershadsky, & Agel, 2002; Heitz, Eisenman, Beck, & Walker, 1999), as well as a difference in proprioceptive ability compared to male counterparts (Park et al., 2008). In terms of overuse injuries, different investigations have reported a higher incidence rate of ilitiobial band friction syndrome in females (Taunton et al.,

2002; DeHaven & Lintner, 1986). A more recent study has shown that females were more than twice as likely to develop ilitiobial band friction syndrome compared to man (Boling et al., 2010). The same study justifies this higher incidence because of the biomechanical differences between genders. In particular, the decreased strength of the lower extremity musculature and altered kinematics and kinetics during dynamic tasks in females.

2.2.3. Age Factor

Knee injuries are likely to occur more frequently in children and young adult individuals. This is intrinsically related with the higher sports participation of these populations. In individuals younger than 25 years old, the most common injury diagnoses are knee strains and sprains (Gage et al., 2012). The youngest athletes may be at a higher risk for knee injuries than their older counterparts, potentially because of sport-specific underdeveloped skills (Jones, Louw, & Grimmer, 2000; Peterson et al., 2000). Although, injuries affecting the knee have also been reported to be the most frequent in veteran athletes (Kallinen & Alén, 1994; Kannus, Niittymäki, Järvinenn & Lehto, 1989). Acute injuries can be relatively common in elderly individuals participating in sport activities which demand high coordination, reaction time and balance capabilities (Kallinen & Markku, 1995). In younger ages, traumatic soft tissue injuries, such ACL tears, are a major predisposing factor for an early onset of knee OA (Muthuri et al., 2011; Roos, 2000). Previous knee injury has also been associated with increased prevalence of knee OA in the athletic and recreationally active "middle-aged" population (Adams et al., 2013) as well, in former impact athletes, like soccer, handball and ice hockey players (Tveit, Rosengren, Nilsson, & Karlsson, 2012). Among former elite athletes the prevalence of lower limb OA has shown to be higher compared to the general population and other occupational sectors (Gouttebarge, Inklaar, Backx, & Kerkhoffs, 2015). However, the current evidence is unclear whether sport participation in the absence of injury accelerates the rate of development of OA (Hunter & Eckstein, 2009). Overuse injuries affecting the knee may also be prevalent in both young (Cuff et al., 2010) and elderly athletic populations (Kannus et al., 1989). Most injuries in older

athletes are chronic and overuse injuries, resulting mainly from the aging physiological decline of soft tissues (Chen, Mears, & Hawkins, 2005). Among younger athletes, patellofemoral pain syndrome and apophysitis of the patella tendon on the tibial tubercule (Osgood-Schlatter disease) are two of the most common overuse injuries (Adirim & Cheng, 2003).

3. Assessment Outcomes Following Knee Injury

The complex structure and functioning of knee presents a challenge for the clinical assessment (Rossi et al., 2011; Solomon, Simel, Bates, Katz, & Schaffer, 2001). When assessing an injured knee or treatment outcomes following a knee injury, often patient-reported outcome (PRO) measures and objective clinical outcome measures are combined (Tanner, Dainty, Marx, & Kirkley, 2007). To be clinically meaningful, these outcome measures must be relevant to the individual or population (Veenhof et al., 2006; Wang, Jones, Khair, & Miniaci, 2010), easy to perform and/or score, and possess adequate psychometric properties (Lysholm & Tegner, 2007). The outcomes provided determine patients' disability and impairment, choice of therapy, and the degree of change over time (Vianin, 2008).

3.1. Patient-Report Outcome Measures

PROs can be generically defined as measurements of any aspect of a patient health status that comes directly from the patient (Food and Drug Administration, 2006). Normally, these measures or instruments consist of questionnaires and rating scales designed to measure patients' perceptions of their general health, or in relation to specific diseases (Guyatt, 1995; Guyatt, Feeny, & Patrick, 1993; Patrick & Deyo, 1989)

or anatomic areas, including the knee (Wright, 2009). In clinical research these instruments play a significant role as primary endpoints for the development and evaluation of new therapies (Willke, Burke, & Erickson, 2004). For appropriate PRO measure selection, the appraisal of the instrument content as well the evidence for psychometric properties in relation to the disease and patient population of interest, are mandatory prerequisites (Fitzpatrick, Davey, Buxton, & Jones, 1998). It has been recommended that general health questionnaires should be used alongside knee specific instruments in patients with knee disorders (Bartlett et al., 2005; Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988; Bombardier et al., 1995). Furthermore, in more physically active individuals, specific instruments to assess physical activity and sport participation are also frequently applied (Della Villa et al., 2010; Faltstrom, Hagglund, & Kvist, 2013; Gobbi, Nunag, & Mallinowski, 2005; McCullough et al., 2012).

3.1.1. General Health Instruments

General (or generic) health outcome measures set out to describe or measure general health in a way that it can be compared to different diseases and conditions across the clinical spectrum (Patrick & Deyo, 1989). This allows researchers to analyse the relative impact of treatment on patients with different diagnoses (Wright, 2009). Also, these instruments have greater potential to measure side-effects or unforeseen effects of treatment, and are more suitable for economic evaluation (Garrat, Brealey, & Gillespie, 2004). In knee conditions, different generic health outcome measures have been reported in the literature (Garrat et al., 2004; Rodriguez-Merchan, 2012; Wright, 2009). Two of the most currently used measures are the Medical Outcomes Study 36-Item Short Form (SF-36) and the EQ-5D (formerly known as the EuroQol index).

3.1.1.1. SF-36

The SF-36 is the most widespread general health outcome measure (Garrat, Schmidt, Mackintosh, & Fitzpatrick, 2002). The SF-36 questionnaire consists of 35 questions in eight subscale domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health) and one general overall health status question. Each subscale score is totalled, weighted, and transformed to fall between 0 and 100 (where 0 is worst possible health, severe disability and 100 is best possible health, no disability) (Patel, Donegan, & Albert, 2007). In patients with OA of the knee the SF-36 has been shown to have a satisfactory reliability and be more responsive than other disease specific instruments (Brazier, Harper, Munro, Walters, & Snaith, 1999). The SF-36 usage has been recommended for patients undergoing knee arthroplasty (Dunbar, Robertsson, Ryd, & Lidgren, 2001) and cartilage implantation (Bartlett et al., 2005).

3.1.1.2. EQ-5D

The EQ-5D was developed by the EuroQol Group in order to provide a simpler, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). This instrument comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The respondent is asked to indicate his/her health state rating of each the 5 dimensions by choosing between 3 levels (no problems, some problems, extreme problems). The EQ-5D also includes the EuroQol visual analogue scale (EQ-VAS), which is a visual analogic scale ranging from 0 to 100 (where 0 is worst imaginable health state and 100 is best imaginable health state), for the patient´s health state that day (EuroQol Group, 1990; Brooks, 1996). The EQ-5D has show acceptable reliability and validity for knee OA (Fransen & Edmonds, 1999) and rheumatoid arthritis (Hurst, Kind, Ruta, Hunter, & Stubbings, 1997).

3.1.2. Knee Specific Instruments

In the past past two decades, there has been a considerable growth in the number of knee specific instruments available (Collins, Misra, Felson, Crossley, & Roos, 2011). Although, there is not a "gold standard" instrument that can be universally applied across the spectrum of knee disorders (Wang et al., 2010). Several reviews have been conducted on knee-specific PRO measures and their characteristics (Garratt et al., 2004; Lysholm and Tegner, 2007; Rodriguez-Merchan, 2012; Wang et al., 2010; Wright, 2009). The most commonly used knee-specific PROs reported in the literature are: i) the Lysholm Knee Function Scale; ii) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); iii) the Knee Injury and Osteoarthritis Outcome Score (KOOS); iv) the International Knee Documentation Committee (IKDC) Subjective Form; and v) the Modified Cincinnati Knee Score (CKS).

3.1.2.1. Lysholm Knee Function Scale

The Lysholm Knee Function Scale was first published in 1982 (Lysholm & Gillquist, 1982) and modified in 1985 (Tegner & Lysholm, 1985). It was developed for the follow-up evaluation of knee ligament surgery, with an emphasis on symptoms of instability. It consists of eight items (limp, support, stair climbing, squatting, instability, locking and catching, pain, swelling) on a 0 to 100 points scale, where 100 represents the best outcome possible. The Lysholm Knee Scale quickly became one of the most widely adopted PRO measures for knee ligament surgery (Wright, 2009) and has been commonly used in conjunction with the Tegner Activity Scale (TAS) (Tegner & Lysholm, 1985). This instrument shows acceptable psychometric properties for several knee conditions, including cartilage disorders (Kocher, Steadman, Briggs, Sterett, & Hawkins, 2004), meniscal injuries (Briggs, Kocher, Rodkey, & Steadman, 2006) and anterior cruciate ligament injuries (Briggs et al., 2009). Although a potentially large ceiling effect is a major limitation of this instrument (Ra et al., 2014), the Lysholm Knee Scale is currently recommended to be used in conjunction with more modern PRO measures (Wright, 2009).

3.1.2.2. WOMAC

The WOMAC is a widely used instrument developed for elderly people with OA (Bellamy et al., 1988). Using visual analog scales, its 24 items probe three dimensions, pain (5 items), stiffness (2 items) and functional difficulty (17 items). The total score and the dimension scores (range: 0–100, with 100 indicating the worst possible state) correspond to the sum of the related items divided by the total number of items considered (Rodriguez-Merchan, 2012). The WOMAC questionnaire has shown good validity, reliability and sensitivity to change and has proved to be efficient when used in OA (Angst, Aeschlimann, Steiner, & Stucki, 2001; Davies, Watson, & Bellamy, 1999; Roos, Klässbo, & Lohmander, 1999). However, since it was designed for older individuals, this instrument may have reduced applicability for younger and physically active populations (Roos & Lohmander, 2003).

3.1.2.3. KOOS

The KOOS has been developed as an extension of the WOMAC. This PRO measure consists of 42 items with 5 separately scored subscales: i) pain (9 items); ii) symptoms (7 items); iii) activities of daily living (17 items); iv) sport and recreation function (5 items); and v) knee-related quality of life. Each item is graded on a five-point Likert scale (0 to 4). Each subscale is summed and transformed to a score of 0 to 100 (where 0 is worst possible and 100 is best possible) (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). This instrument capacity of providing differentiated subscale scores in addition to the overall score is an advantage in comparison to other knee specific instruments. Furthermore, the sport related subscale score makes the KOOS suitable to younger, more physically active populations (Hambly & Griva, 2010). Additionally, it has greater responsiveness comparatively to other instruments, such as the WOMAC (Roos & Lohmander, 2003). The KOOS has been validated for multiple knee conditions such as ACL reconstruction (Salavati, Akhbari, Mohammadi, Mazaheri, & Khorrami, 2011), focal cartilage injuries (Bekkers, de Windt, Raijmakers, Dhert, & Saris, 2009), meniscectomy (Roos et al., 1998) and total knee replacement (Roos & Toksvig-Larsen, 2003). Besides, it is widely used as a treatment outcome

measure in knee injured athletes (Hill & O'Leary, 2013; Hoch, Druvenga, Ferguson, Houston & Hoch, 2015; Shaha et al., 2013). Although, there is a paucity in normative KOOS values for athletic populations (Cameron et al., 2013). The only normative values currently available for these populations are for amateur soccer players (Frobell et al., 2008), young individuals entering the military academy (Cameron et al., 2013), and for downhill runners (Roi, Monticone, Salvoni, Sassi, & Alberti, 2015).

3.1.2.4. IKDC Subjective Form

The IKDC Subjective Form was created by a committee of international knee experts from the American Orthopedic Society for Sports Medicine and the European Society for Sports Traumatology, Knee Surgery and Arthroscopy. The Subjective Form is a knee-specific instrument developed to measure symptoms, function and sports activities in patients who have one or more of a variety of knee conditions (Irrgang et al., 2001). This instrument is a single-index score consisting of 18 items. The form can be scored when 16 of the 18 of the questions are answered (90%). The raw scores are summed and transformed to a scale of 0 to 100 (where 100 is the best possible score) (Wright, 2009). The subjective form has been validated and shown to be reliable for multiple knee conditions (Irrgang et al., 2006), including ACL reconstruction (van Meer et al., 2013), meniscal injuries (van de Graaf, Wolterbeek, Scholtes, Mutsaerts, & Poolman, 2014) and acute patellar dislocation (Paxton, Fithian, Stone, & Silva, 2003). This instrument has also shown responsiveness for a broad range of knee conditions, with an increase in score of 11.5 points, potentially representing an improvement in condition (Irrgang et al., 2006).

3.1.2.5. Modified Cincinnati Knee Score

The CKS was first described in 1983 (Noyes, Matthews, Mooar, & Grood, 1983). Originally it assessed subjective symptoms and functional activity level, with 50 points assigned to each, for a total of 100 points. This was later modified to a 100 points

six-subscale scoring system (where 100 is the best score possible): i) symptoms; ii) daily and sports functional activities; iii) physical examination; iv) knee stability testing; v) radiographic findings; and vi) functional testing (Barber-Westin, Noyes, & McCloskey, 1999). The main criticism towards this instrument is the recommendation of independent examiners rather that patient-reported self-assessment (Roos, 2000). This PRO measure has shown reliability, validity, and responsiveness for anterior ACL reconstruction (Barber-Westin et al., 1999), being predominantly used in this type injury (Risberg, Holm, Steen, & Beynnon, 1999; Shelbourne, Benner & Gray, 2014) and in articular cartilage lesions (Gillogly & Arnold, 2014).

3.1.3. Physical Activity Instruments

Physical activity measures are commonly used to evaluate physical activity and sports participation in epidemiological studies (Dishman, Heath, & Lee, 2012). As mentioned, a significant risk factor for knee injury is the physical activity profile, with most injuries occurring while performing sports (Ferry, Bergstrom, Hedstrom, Lorentzon, & Zeisig, 2014; Gage et al., 2012; Maes et al., 2002). The main aim of the majority of active individuals and athletes with knee injury, is to return to their pre-injury physical activity and sport participation level without limitations. Thus, when assessing treatment outcomes in these populations, clinicians and researchers often use specific physical activity PRO measures in addition to knee specific and general health instruments (Wright, 2009). Two of the most used knee specific physical activity instruments are the TAS and the Marx Activity Rating Scale (ARS). Several studies have also used more general instruments, such as the Modified Baecke Questionnaire (Oussedik, Tsitskaris, & Parker, 2015; Pestka, Bode, Salzmann, Sudkamp, & Niemeyer, 2012; van Assche et al., 2009). However, since there is not a consensual instrument or set of instruments, there are considerable discrepancies in the literature on reporting physical activity and sports participation following knee injury (Chalmers, Vigneswaran, Harris, & Cole, 2013; Dahm, Sunni, Harrington, Sayeed, & Berry, 2008; Papalia, Del Buono, Zampogna, Maffulli, & Denaro, 2012).

3.1.3.1. Tegner Activity Scale

The TAS is a single item instrument designed as a score of activity level to complement the Lysholm Knee Functional Scale for patients with ligamentous injuries (Lysholm & Gillquist, 1982; Tegner & Lysholm, 1985). It scores a person's activity level between 0 to 10 where 0 is "on sick leave/disability" and 10 is "participation in competitive sports such as soccer at a national or international elite level" (Tegner & Lysholm, 1985). TAS is the most widely used activity scoring system for patients with knee disorders. Alongside the Lysholm scale, TAS has shown acceptable psychometric properties for meniscal injuries (Briggs et al., 2006) and anterior cruciate ligament injuries (Briggs et al., 2009). In spite of its wide use and possible advantage of retrospective assessment, caution is advised in the interpretation of TAS scores, since it does not provide any qualitative information regarding intensity and frequency of the physical activity or sport participation. Moreover, as described for articular cartilage repair, the TAS data has been inconsistently reported in the literature, with methodological detail lacking (Hambly, 2011b).

3.1.3.2. Marx Activity Rating Scale

The Marx ARS was designed to be a short patient-reported physical activity assessment that could be used in addition to knee specific instruments and general health outcome measures (Wright, 2009). The scale is designed to assess the individual's highest peak activity over the past year (Marx, Stump, Jones, Wickiewicz, & Warren, 2001). It consists of four items: i) "running"; ii) "cutting"; iii) "decelerating"; and iv) "pivoting". These items are scored from 0 to 4, according to frequency performed, from less than once per month (0 points) to four or more times per week (4 points). The minimum score is 0 and the maximum 16 points. In terms of psychometric properties, this scale has been reported to satisfy the reliability, validity and responsiveness criteria for a population of athletic individuals with knee a disorder (Marx et al., 2001). Although, the score change equivalent to a significant change in activity level is unclear (Wright, 2009).

3.1.3.3. Modified Baecke Questionnaire

The Modified Baecke Questionnaire (Voorrips, Ravelli, Dongelmans, Deurenberg, & Van Staveren, 1991) is an adapted version of the physical activity questionnaire of Baecke and co-workers (Baecke, Burema, & Frijters, 1982) developed for the elderly population. This instrument consists of 10 items, within 3 indices or subscales: i) "household activities"; ii) "sport activities"; and iii) "leisure time activities". Each subscale has a different grading score system. The total score is calculated as a sum of the 3 subscales, and the maximum score is 15. Despite the questionnaire being designed for older individuals and its psychometric properties have not having been tested for any knee condition, it has been particularly used following cartilage repair procedures of the knee (Oussedik, Tsitskaris, & Parker, 2015; Pestka et al., 2012; van Assche et al., 2009).

3.2. Objective Clinical Outcome Measures

In general, the objective clinical outcomes following knee injury encompass the physical examination (Rossi et al., 2001), radiological measures analysis (Frobell et al., 2009; Lee et al., 1996), joint range of motion assessment (Irrgang & Harner, 1995), muscle strength assessment (Thomee et al., 2011) and joint laxity tests (Shultz, Dudle, & Kong, 2012). Functional performance (Herbst et al., 2015; Gustavsson et al., 2006) and cardiorespiratory fitness tests (Olivier et al., 2010; Olivier et al., 2008) may also be relevant outcomes, particularly for athletic populations.

3.2.1. Cardiorespiratory Deconditioning

As previously mentioned, traumatic knee injuries that require surgery and long periods of rehabilitation, such as ACL tears, are relatively common in sports (Kujala et al., 1995; Loes et al., 2000; Majewski et al., 2006; Ristolainen et al., 2010). Following knee surgery, commonly there is a medical counter indication to use the injured limb during the time required for the healing (Olivier et al., 2010). For example, individuals who have undergone ACL reconstruction may only return to light sporting activities such as running, 2–3 months after surgery and to contact sports, including cutting and jumping, not before 6 months (Kvist, 2004; van Grinsven, van Cingel, Holla, & van Loon, 2010). In elite soccer athletes, the mean return time to normal training is not less than 5 months (Zaffagnini et al., 2014) with the return to competition happening between 6-8 months after surgery (Roi, Nanni and Tencone, 2006; Walden, Hagglund, Magnusson, & Ekstrand, 2011; Zaffagnini et al., 2014). Other knee surgeries such as posterior cruciate ligament reconstructions or ACI procedures are associated with even longer periods of rehabilitation and delayed return to sport (Della Villa et al., 2010; Fanelli, 2008; Mithoefer et al., 2012).

The substantial reduction or absence of training stimulus following a severe knee injury results in partial or complete loss of the previously acquired physiological and performance adaptations. This gradual physical deconditioning process is generally described as detraining (Mujika & Padilla, 2000a; Mujika & Padilla, 2000b). Detraining substantially affects the cardiac morphology and function (Figure 2); thus, its impact on cardiorespiratory performance are particularly relevant for endurance athletes following a severe knee injury and/or surgery (Olivier et al., 2010; Olivier, Legrand, Rogez, Berthoin, & Weissland, 2007). Nevertheless, most of the evidence gathered on detraining has been based on voluntary training refrains, off season breaks (Mujika & Padilla, 2003) and bed rest studies (Lee, Moore, Everett, Stenger & Platts, 2010). Therefore, few studies have been conducted using clinical models (Olivier et al., 2010; Olivier et al., 2008; Steding-Ehrenborg, Heden, Herbertsson, & Arheden, 2013). In trained runners, 15 days of training refrain has been reported to induce a 5 % decrease (Houmard et al., 1992), and 3-8 weeks a 20 % drop, in maximal oxygen uptake (VO_{2max}) (Martin, Coyle, Bloomfield, & Ehsani, 1986). In football players, a 4 % VO_{2max} decrease was observed after 3 weeks of post-season break (Bangsbo & Mizuno,

1988). The VO_{2max} loss during training absence seems to be dependent on time and initial fitness level. Longer periods of training cessation and higher aerobic capacity are associated with greater losses in cardiorespiratory fitness (Mujika & Padilla, 2001a; Mujika & Padilla, 2003). One of the few clinical studies published, which was conducted in soccer players following ACL reconstruction, has reported a significant drop in single-leg cycling (SLC) peak oxygen uptake (VO_{2peak}) after 6 weeks of a standard rehabilitation programme (Olivier et al., 2010). For short periods of training cessation, the decrease in maximal aerobic capacity is mainly attributed to a decline in stroke volume arising from a blood volume reduction (Coyle et al., 1984). To compensate for this blood volume reduction, heart rate (HR) at both submaximal and maximal intensities may increase by approximately 5-10 % (Mujika & Padilla, 2003). A clinical study conducted with soccer players who underwent knee surgery has shown a 22 % decrease in resting stroke volume within a 7-day interval before and after hospitalisation (Olivier et al., 2007).

In terms of cardiac morphology, training cessation has a particularly negative effect on ventricular volumes (Mujika & Padilla, 2000b). A recent study showed that the cardiac deconditioning following an ACL injury resulted in a 3 % decrease of the total heart volume, as well as reductions in left and right ventricular end-diastolic volumes. (Steding-Ehrenborg et al., 2013). The physical activity restraint following voluntary or forced training cessation also results in peripheral deconditioning (Mujika & Padilla, 2001b). Although, changes at the muscle level are likely to occur later than central deconditioning (Mujika & Padilla, 2003). Reductions in muscle capillary density, oxidative capacity and mean fiber cross-sectional area have all been documented in athletes detraining (Mujika & Padilla 2001b, 2000a, 2000b).

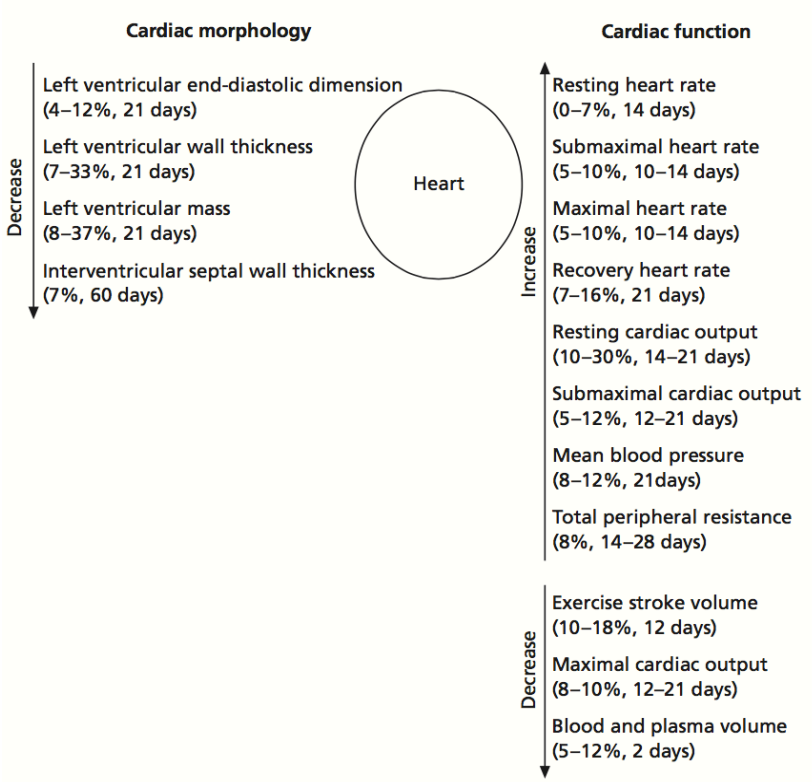


Figure 2 - Cardiac morphological and physiological changes associated with detraining (from Mujika & Padilla, 2003, p. 122)

3.2.2. Cardiorespiratory Fitness Testing

Cardiopulmonary exercise testing is an important outcome to objectively monitor the cardiorespiratory fitness deconditioning and reconditioning following a severe knee injury and throughout rehabilitation. (Olivier et al., 2008). It may also contribute to establishing and implementing individualised high-intensity cardiorespiratory training programmes sooner in the rehabilitation progression, thus accelerating the cardiorespiratory reconditioning in athletic populations (Olivier et al., 2010). Nevertheless, in the early rehabilitation stages of a severe knee injury and/or injury, traditional cycling and treadmill exercises are usually contraindicated, due to tissue healing process, limited joint range of movement and limb weight bearing

restrictions (Kvist, 2004; van Grinsven et al., 2010). To overcome these limitations, exercise testing and training modalities involving smaller muscular mass, such as arm cranking or SLC with the non-injured limb have been used in the rehabilitation context (Olivier et al., 2010; Olivier et al., 2008). Comparatively to whole body exercise, small muscle mass exercise induces lower cardiovascular and metabolic responses, since it is peripherally limited (Davies & Sargeant, 1975; Neary & Wenger, 1986; Saltin et al., 1976). Depending on the population, both arm crank and SLC maximal exercise may elicit 85 % of the VO_{2peak} and over 90 % of the peak HR (HR_{peak}) attained during double-leg cycling (Klausen, Secher, Clausen, Hartling, & Trap-Jensen, 1982; Neary & Wenger, 1986; Olivier et al., 2008; Rud, Foss, Krustrup, Secher, & Hallen, 2012; Secher & Volianitis, 2006), with the highest responses typically being induced by SLC (Shiomi, Mauyama, Saito, & Umemara, 2000). Furthermore, SLC has been shown to elicit lower perceived exertion levels and lower blood lactate concentration, thus making it better tolerated and more indicated for patients following knee surgery (Olivier et al., 2008). Reduced weight bearing exercise modalities, such as lower-body positive pressure (Raffalt, Hovgaard-Hansen, & Jensen, 2013) or aquatic treadmill running (Rife et al., 2010) can also be used for exercise testing and training purposes in individuals with knee injury. However, for the aforementioned reasons they may not be possible or safe to perform during the early stages of rehabilitation.

3.2.2.1. Single-Leg Cycling

Following an early research impetus on SLC to study haemodynamics (Freyschuss & Strandell, 1968) and the cardiovascular limitations of maximal exercise (Davies & Sargeant, 1975; Klausen et al. 1982; Saltin et al., 1976), in the last 15 years, SLC exercise testing and training has been applied for clinical purposes. SLC has been used in individuals following knee surgery (Olivier et al., 2010; Olivier et al., 2008), in patients with lower-limb amputations (Wezenberg, de Haan, van der Woude and Houdjik, 2012), and particularly, in patients with chronic obstructive pulmonary disease (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006). Commonly, SLC exercise testing is performed using classical incremental graded exercise test (GXT) protocols. These protocols consist of

continuous, linearly or step-wise applied fixed power output increments, ranging between 10-16 W per minute. The protocol lasts until the individual reaches volitional exhaustion (Bell, Neary, & Wenger, 1988; McPhee, Williams, Degens, & Jones, 2010; Neary & Wenger, 1986; Ogita, Stam, Tazawa, Toussaint, & Hollander, 2000; Rud et al., 2012). However, some studies conducted in clinical populations have reported longer incremental steps (Olivier et al., 2010; Olivier et al., 2008) or lower power output increments (Bjorgen et al., 2009a; Bjorgen et al., 2009b). A discontinuous GXT protocol has been also reported to be feasible and valid for older individuals with lower-limb amputation (Wezenberg et al., 2012).

3.2.2.2. Counterweighted Single-Leg Cycling

Due to its unilateral nature, SLC requires an active pull phase of the pedal cycle, which imposes an increased activation and fatigue on the leg muscles, particularly the hip flexor muscles (Bini, Jacques, Lanferdini, & Vaz, 2015). This may cause coordination difficulties and distorted cycling rhythm (Burns, Pollock, Lascola, & McDaniel, 2014a). To diminish the awkwardness and peripheral discomfort associated with SLC, different assisting systems or devices have been applied such as: tandem cycling (Gleser, 1973); springs system (Freyschuss & Strandell 1968); electric motor (Koga et al., 2001); and a fixed-flywheel (Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006; Rud et al., 2012). More recently, a 10 kg (≈ 97 N) counterweight attached to the non-exercising arm crank (Figure 3) has been used (Abbiss et al., 2011; Burns et al., 2014a; Thomas, 2009). At sub-maximal work rates, this counterweight setting has been shown to elicit similar cardiovascular responses to double-leg cycling for the same work rate (Burns et al., 2014a). Nevertheless, the effect of a 10 kg counterweight or any other mass during SLC exercise testing has not yet been acknowledged in previous research.

Figure 3 - 97 N counterweight device attached to the non-exercising arm crank
(from Burns et al., 2014a, p. 963)

3.2.2.3. Self-Paced Protocols

In recent years, to overcome the rigidity of the GXT protocols (Noakes, 2008), SPT has emerged as a valid alternative for maximal exercise testing. Evolving from previous research on sub-maximal perceptually regulated exercise testing (Eston, Faulkner, Mason, & Parfitt, 2006; Eston, Lamb, Parfitt, & King, 2005; Eston, Lambrick, Sheppard, & Parfitt, 2008), a maximal SPT was originally described by Mauger and Sculthorpe (2012). Their study was performed using double-leg cycling and the SPT protocol design consisted of 5x2 min stages protocol clamped to progressively ordered rate of perceived exertion (RPE) levels (11, 13, 15, 17 and 20) from the 6-20 Borg Scale (Borg, 1970) (Figure 4). The SPT allows individuals to pace themselves by continuously adjusting their work rate to match those RPE levels. The progressive RPE clamps enables the SPT to retain an incremental format as the GXT. Following the original investigation of Mauger and Scultorphe (2012), other studies have been published on maximal self-paced testing concept, both in cycling (Chidnok et al., 2013a) and treadmill running exercise testing (Faulkner, Mauger, Woolley, & Lambrick, 2015; Hogg, Hopker, & Mauger, 2015; Mauger, Metcalfe, Taylor, & Castle,

2013). The evidence gathered from these studies suggests that self-paced testing may elicit similar or even higher VO_{2max} than conventional GXTs (Chidnok et al., 2013a; Mauger & Sculthorpe, 2012). However, the ability of the SPT to generate the highest VO_{2max} is debateable (Chidnok et al., 2013b; Mauger, 2013). Due to the increased peripheral stress associated with SLC, the SPT's short duration, closed-loop design and the individually orientated subjective intensities, could be beneficial for SLC exercise testing.

Rating	Descriptor
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 4 - Rate of perceived exertion 6-20 Borg Scale

(from Borg, 1998)

3.3. Psychometric Properties

The most relevant psychometric properties that are required for health related outcome measures are reliability, validity and responsiveness (de Vet, Terwee, Mokkink, & Knol, 2011). These properties are closely associated with the population and testing context, therefore they refer to the results obtained from a measurement and not to the instrument itself (Steiner & Norman, 2008). Alongside adequate psychometric properties, interpretability is also an important characteristic of a PRO measure. Interpretability refers to the degree to which one can assign qualitative meaning to an instrument's quantitative scores or change in scores (Mokkink et al., 2010). This characteristic can be assessed by comparing individual or group results to normative data and estimate the minimal important and detectable changes (Impellizzeri & Marcora, 2009).

3.3.1. Reliability

Before one uses an instrument, it should be established whether it is measuring "something" in a reproducible manner (Keszei, Novak, & Streiner, 2010). The reliability reflects how consistent or reproducible the instrument is when administered properly (Lysholm & Tegner, 2007). Reliability is not a fixed property of an instrument. An instrument that is reliable in one set of circumstances may not be reliable under different conditions. There are different indices and methodologies to measure reliability, and not all are applicable to a given instrument or clinical setting (Keszei et al., 2010).

3.3.1.1. Internal Consistency

Internal consistency is defined as the degree of interrelatedness among items of an instrument. More specifically, it measures the average correlation among all or a group of items of a PRO measure (Keszei et al., 2010). Internal consistency is commonly measured by the Cronbach's alpha (Cronbach, 1951) or the split half-method (Steiner & Norman, 1998). These measures do not take into account the variations in time or between observers, and therefore yield an optimistic estimate of the true reliability of the test. Another major problem with these indices is that they are sensitive not only to the internal consistency of the scale, but to its length (Keszei et al., 2010).

3.3.1.2. Test-Retest Reliability

Test-retest reliability assesses the degree of stability of a measurement, either over time or between different observers (Lysholm & Tegner, 2007). In sports medicine, two sub-types of re-test reliability have been described, the absolute and the relative reliability (Atkinson & Nevill, 1998). The absolute reliability refers to the degree to which repeated measures vary for individuals. The relative reliability is the degree to which individuals maintain their position in a sample with repeated measurements (Atkinson & Nevill, 1998). When tests are used to discriminate between individuals (cross-sectional assessment), parameters of relative reliability should be used (i.e., intraclass correlation coefficient, ICC). Parameters of absolute reliability (i.e., standard error of measurement, SEM) are required for evaluative tests to monitor changes over time (longitudinal assessment) (de Vet, Terwee, Knol & Bouter, 2006). The distinction between absolute and relative reliability should be considered when reporting reliability data (Impellizzeri & Marcora, 2009).

3.3.2. Validity

Assessing the reliability of an outcome measure is not sufficient, its validity should be also assessed. Validity is a way of describing whether an instrument measures what it purports to measure (Lysholm & Tegner, 2007). As with reliability, validity is not an inherent property of the measurement but an interaction of the instrument, the group being tested, and the conditions (Keszei et al., 2010). There are different methods and 'types' of validity, which are based on the inherent characteristics of the measure and its relation to a criterion or a construct (Impellizzeri & Marcora, 2009). Validity is typically divided into content validity, criterion validity, and construct validity (Mokkink et al., 2010). The selection of the most appropriate method for validating a test will depend on its purpose (discriminative or evaluative) and its application (research or routine practice) (Impellizzeri & Marcora, 2009).

3.3.2.1. Content Validity

Content validity reflects the degree to which an instrument represents a specific sphere of concept. Unlike other forms of validation, there is no correlation coefficient or some other statistical approach that can be used to measure content validity (Keszei et al., 2010). Content validity depends only on subjective judgments, and therefore should not be the only criterion of validity. The simplest form of content validity is called face validity, which may involve the opinion of a single expert (Lysholm & Tegner, 2007).

3.3.2.2. Criterion Validity

Criterion validity reflects how well the new measure correlated with a widely accepted measure of the same characteristics - the "gold standard" (Mokkink et al., 2010). A correlation larger than 0.70 between the new measure and the reference measure is conventionally used as benchmark for construct or criterion validity (Terwee

et al., 2007). If the comparison of the two measures is performed at the same time, it is called concurrent validation. If the criterion measure is performed later, the new test is evaluated by how well it predicts the criterion score. This type of validity is called predictive validity (Keszei et al., 2010). In some situations, when a gold-standard outcome measure does not exist, this type of validity is not possible to perform.

3.3.2.3. Construct Validity

Construct validity shows how well the instrument measures the theoretical construct that it was designed to measure (Lysholm & Tegner, 2007). To establish construct validity, one has to generate hypothesis based upon a theoretical construct. These hypotheses are then tested to give support to the validity of the instrument (Keszei et al., 2010). When testing the hypotheses, it is important that these should be specific and include the magnitude and direction of the expected correlations (Mokkink et al., 2010).

3.3.3. Responsiveness

Responsiveness can be classified as external and internal (Impellizzeri & Marcora, 2009). The first, is also termed as longitudinal validity of the test and refers to the ability of a test to measure changes in the reference measure (Husted, Cook, Farewell & Gladman, 2000). The internal responsiveness is also called sensitivity to change and refers to the ability of a measure to change over a particular time frame (Impellizzeri & Marcora, 2009). The methods frequently reported to calculate the internal responsiveness are: i) Cohen's effect size; ii) standardized response mean; and iii) Guyatt's responsiveness index (Husted et al., 2000). Both effect size and standardised response mean are commonly applied to describe the responsiveness of the PRO measures for the knee (Collins et al, 2011).

4. Literature Review Summary

The assessment of physically active individuals with knee injury often combines PRO measures, with more objective measures. The literature review conducted for this thesis, identified aspects that remain unclear or have not been investigated in previous research, regarding the use of PRO measures, and also related with the cardiorespiratory fitness assessment following knee injury. In terms of the PRO measures, despite of its widespread use, the literature shows significant discrepancies in reporting physical activity and return to sport following cartilage repair procedures, particularly following ACI. This is important, since return to sport is one the main reasons to elect this cell-based surgery. Moreover, an injury or condition specific critical analysis of these instruments, from a rehabilitative perspective, has not been provided in previous research. This information could be useful for the rehabilitation team when electing PRO measures. Another limitation of the literature is related with the paucity in normative values of PRO instruments for athletic populations. This is a particularly important limitation of the KOOS, since this multidimensional instrument, which includes a sport and recreation subscale, is commonly used in athletes with knee injury and/or following knee surgery. Currently, regardless of the high incidence of knee injuries in recreational long-distance runners, there are not published normative KOOS values for marathon runners. The existence of such values could be a useful self-reported measure of treatment outcomes for this population. Concerning the cardiorespiratory fitness assessment, SLC exercise testing is an exercise modality used when conventional bilateral exercise is contraindicated or not possible to perform. However, only traditional fixed-rate incremental protocols have been described in previous SLC research. Therefore, the potential of perceptually regulated protocols for SLC exercise testing has not yet been acknowledge, as well the effect of counterweight-assisted SLC on maximal cardiorespiratory responses. The literature limitations and gaps mentioned were addressed in this thesis studies' research questions, aims and hypothesis.

5. Aims and Outline of the Thesis

The present thesis comprises five studies, divided into two distinct parts. The first part (Part I) addressed the patient-reported measures of knee function and sport participation, and the second part (Part II) was focused on SLC exercise testing.

The specific aims of Part I were:

Chapter 1: To identify the patient-reported instruments that are commonly used in the evaluation of physical activity and return to sport following ACI, and to provide a critical analysis of these instruments from a rehabilitative perspective.

Chapter 2: To provide normative reference values for the KOOS for recreational marathon runners, of differing age groups and RRI history.

The specific aims of Part II were:

Chapter 1: To assess the reliability of a SPT in SLC exercise testing.

Chapter 2: To assess the validity of a SPT in SLC exercise testing.

Chapter 3: To assess the effect of a 10 kg counterweight on cardiorespiratory, metabolic and perceptual responses during SLC exercise testing.

All study chapters are either published or are in the process of finalisation for submission. Therefore, there is a necessary overlap in the contents of these manuscripts. This overlap is particularly noticeable in Part II. Furthermore, the publications from this PhD can be found in the Appendices.

PART I

PATIENT-REPORTED MEASURES OF THE KNEE AND PHYSICAL ACTIVITY

CHAPTER 1: MEASURING PHYSICAL ACTIVITY AND SPORTS PARTICIPATION FOLLOWING AUTOLOGOUS CARTILAGE IMPLANTATION: A SYSTEMATIC REVIEW

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1. Abstract

The assessment of physical activity and return to sport and exercise activities is an important component in the overall evaluation of outcome following autologous cartilage implantation (ACI). The aims of this investigation were to systematically review the patient-reported instruments that are commonly used in the evaluation of physical activity and return to sport following ACI, and provide a critical analysis of these instruments from a rehabilitative perspective. A computerized search was performed in January 2013 and repeated in March 2013. The inclusion criteria included: (1) studies written in English and published between 1994 and 2013; (2) clinical studies where knee ACI cartilage repair was the primary treatment, or comparison studies between ACI and other techniques, or between different ACI generations; (3) studies reporting postoperative physical activity and sport participation outcomes results; and lastly (4) studies with evidence level between I and III. Twenty-six studies fulfilled the inclusion criteria. Three physical activity scales were identified: Tegner Activity Scale, the Modified Baecke Questionnaire, and the Activity Rating Scale. Five knee-specific instruments were identified: Lysholm Knee Function Scale, the International Knee Documentation Committee Score Subjective Form, the Knee Injury and Osteoarthritis Outcome Score, the Modified Cincinnati Knee Score, and the Stanmore-Bentley Functional Score. This systematic review found considerable heterogeneity in reporting physical activity and sports participation following ACI. Current instruments do not fulfil the rehabilitative needs in the evaluation of physical activity and sports participation. The validated instruments fail in the assessment of frequency, intensity, and duration of sports participation.

2. Context

Acute and chronic articular cartilage lesions can lead to severe limitation of physical activity and sports participation, and an increased risk of early degenerative changes and disability (Alford & Cole, 2005; Heir et al., 2010; Mandelbaum et al., 1998). The prevalence of articular cartilage lesions is often higher in individuals who participate in sports activities (Widuchowski, Widuchowski, & Trzaska, 2007). These lesions not only affect high-level competitive athletes (Aroen et al., 2004; Flanigan, Harris, Trinh, Siston, & Brophy, 2010), but also recreational athletes, especially those involved in pivoting sports (Mithoefer et al., 2012). Autologous chondrocyte implantation (ACI) is a chondrocyte-based surgical technique developed in Sweden in the 1980s for the treatment of cartilage injuries (Petersen, 2003). Since the first published clinical study in 1994 (Brittberg et al., 1994), several different generations of the ACI technique have been developed (Benthien & Behrens, 2011; Filardo et al., 2012; Haddo et al., 2004; Keeney, Lai, & Yang, 2011; Steinwachs, 2009). Comparatively to other surgical techniques the ACI is the preferred treatment for younger active patients with large articular cartilage defects, short duration of symptoms, and no previous cartilage surgery (Harris, Siston, Pan, & Flanigan, 2010). The assessment of physical activity and sports engagement is extremely important following ACI since return to sports and an exercise activity is one of the main reasons for electing to undergo ACI (Hambly, 2011a). Moreover, for many patients their goal is to return to a pre-injury sports level (Harris, et al., 2010; Mithoefer et al., 2012; Della Villa et al., 2010). Self-reported physical activity questionnaires or interviews are commonly used to measure physical activity and sports participation (Dishman et al., 2012). There is currently no agreement regarding a gold standard patient-assessed measure to follow-up the effects of a cartilage repair surgery (Hambly & Griva, 2010). For ACI patients or for cartilage repair patients as a whole there are no disease-specific or population specific self-reported outcomes. The instruments that have been applied to measure physical activity in this population were originally developed for other knee injuries. Moreover, only two instruments, the International Knee Documentation Committee Score (IKDC) Subjective Form and the Knee Injury and Osteoarthritis Outcome Score (KOOS) are currently validated for a cartilage repair population

(Bekkers et al., 2009; Engelhart et al., 2012) but not specifically for ACI patients. There is a potential overlap between these instruments, since both provide an overall score of the patient's perception of their knee. The discrepancies on reporting physical activity and sports participation following ACI seen in the literature make the understanding and the usefulness of these instruments unclear.

3. Objectives

The objectives of this review are to identify the patient-reported instruments that are commonly used in the evaluation of physical activity and return to sport following ACI and provide a critical analysis of these instruments from a rehabilitative perspective. We hypothesized that the instruments currently used following ACI do not meet the rehabilitative needs of a sporting population.

4. Evidence Acquisition

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) and the Cochrane Handbook for Systematic Reviews (Green & Higgins, 2009).

Search Strategy

The electronic search was undertaken independently by both authors in January 2013 and repeated in March 2013 for validation. The following databases were utilised: PubMed (Medline), the Cochrane Central Register of Controlled Trials, Cumulative

Index for Nursing and Allied Health Literature (CINAHL), SportDiscus™, and Physiotherapy Evidence Database (PEDro). The electronic search strategy used was "(((“physical activity” OR “sport*” OR “functional” OR "activity scale" OR "sports scale" OR "activity rating" OR "sports rating") AND ("knee" OR “knee injury” OR “knee surgery”)) AND ("cartilage repair" OR “chondral repair” OR “chondrocyte implantation” OR “chondrocyte transplantation” OR "MACI” OR “MACT” OR "ACI" OR "CACI" OR "PACI" OR “CCI” OR “ACT” OR "AMIC" OR "Hyalograft C" OR "CaRes"))”. The search period was from January 1, 1994 to March 1, 2013. All searches were carried out with the following inclusion and exclusion criteria.

The inclusion criteria included:

i) English language clinical studies published between 1994 and 2013;

ii) Studies where the primary knee surgical treatment was ACI cartilage repair procedure without any other concomitant surgeries;

iii) Comparison studies of any generation of ACI with any cartilage repair or restoration technique;

iv) Comparison studies of any generation of ACI with a different generation of ACI;

v) Studies reporting postoperative physical activity and sport participation outcomes results;

vi) Therapeutic type studies with level of evidence of I, II or III according to the Oxford Centre for Evidence-based Medicine (Table 1);

Table 1 - Evidence Levels from the Oxford Centre for Evidence-based Medicine*

Evidence Level	Type of study	Characteristics of the study
I.A	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity) of RCTs
	Prognosis	SR (with homogeneity) of inception cohort studies; CDR validated in different populations
	Diagnosis	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
	Differential diag/symptom prevalence	SR (with homogeneity) of prospective cohort studies
	Economic and decision analyses	SR (with homogeneity) of Level 1 economic studies
I.b	Therapy/Prevention, Aetiology/Harm	Individual RCT (with narrow Confidence Interval)
	Prognosis	Individual inception cohort study with > 80% follow-up; CDR validated in a single population
	Diagnosis	Validating cohort study with good reference standards; or CDR tested within one clinical centre
	Differential diag/symptom prevalence	Prospective cohort study with good follow-up
	Economic and decision analyses	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
I.c	Therapy/Prevention, Aetiology/Harm	All or none
	Prognosis	All or none case series
	Diagnosis	Absolute SpPins and SnNouts
	Differential diag/symptom prevalence	All or none case-series
	Economic and decision analyses	Absolute better-value or worse-value analyses
II.a	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity) of cohort studies
	Prognosis	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
	Diagnosis	SR (with homogeneity) of Level >2 diagnostic studies
	Differential diag/symptom prevalence	SR (with homogeneity) of 2b and better studies
	Economic and decision analyses	SR (with homogeneity) of Level >2 economic studies
II.b	Therapy/Prevention, Aetiology/Harm	Individual cohort study (including low quality RCT; e.g., <80% follow up)
	Prognosis	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split sample only
	Diagnosis	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases
	Differential diag/symptom prevalence	Retrospective cohort study, or poor follow-up
	Economic and decision analyses	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses

Table 1 (cont.)

Evidence Level	Type of study	Characteristics of the study
II.c	Therapy/Prevention, Aetiology/Harm	"Outcomes" Research; Ecological studies
	Prognosis	"Outcomes" Research
	Diagnosis	
	Differential diag/symptom prevalence	Ecological studies
	Economic and decision analyses	Audit or outcomes research
III.a	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity) of case-control studies
	Prognosis	
	Diagnosis	SR (with homogeneity) of 3b and better studies
	Differential diag/symptom prevalence	SR (with homogeneity) of 3b and better studies
	Economic and decision analyses	SR (with homogeneity) of 3b and better studies
III.b	Therapy/Prevention, Aetiology/Harm	Individual Case-Control Study
	Prognosis	
	Diagnosis	Non-consecutive study; or without consistently applied reference standards
	Differential diag/symptom prevalence	Non-consecutive cohort study, or very limited population
	Economic and decision analyses	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.

CDR, clinical data repository; RCTs, randomized control trial; SR, systematic review;
*Adapted from Phillips et al., 2009

The exclusion criteria were:

i) Non-English language studies;

ii) Review studies;

iii) In vitro, animal and non-clinical studies;

iv) Studies where the ACI procedure was not performed;

v) Studies reporting data exclusively from ACI procedures in the patellofemoral joint;

vi) Studies with osteoarthritic populations.

Study Selection

A process of study selection was implemented across all studies resultant from the search strategy. First, all duplicates, review studies and papers not in the English language were excluded. The abstracts of the remaining citations were then reviewed for potential eligibility against the inclusion and exclusion criteria. In cases in which the abstracts did not give full information about the inclusion criteria for this review, the full-text versions of the studies were reviewed. Following review of the full-text articles, those studies that met the inclusion criteria were included within the systematic review. All studies identified were independently reviewed by both researchers and checked for potentially inclusive references. The first author was responsible for the final inclusion/exclusion decision in case of disagreement. In addition, reference lists of relevant studies were reviewed to identify studies not found through the primary electronic searches.

Quality Assessment

The quality of the studies as previously referred in the inclusion criteria was assessed by both researchers using the levels of evidence from the Oxford Centre for Evidence-Based Medicine (Phillips et al., 2009). The evidence levels for each study where assigned following determining the primary research question and establishing

the study type. Only therapeutic type studies with levels of evidence between III and I were included.

Data Extraction

The data from the selected studies was extracted and compiled in tabular form by both authors. The data extracted from each eligible study included: surgical procedure(s), maximum follow-up and intermediate assessments, demographics (number of patients, gender and age) and the self-reported PA and sport participation instruments used at each assessment.

5. Evidence Synthesis

Study Selection

The initial search of all databases used yielded 721 citations, the flow chart in Figure 5. summarises the selection process algorithm via PRISMA guidelines (Moher et al., 2009). After the removal of duplicates, reviews, non-English, in vitro, animal, non-clinical papers and studies reporting different cartilage techniques from ACI, 74 studies were included for possible review. Following the review of the full-text of these abstracts, 3 studies reporting patellofemoral joint ACI and 1 study in osteoarthritic population were removed, and 46 studies were removed since the evidence level provided was > III. The remaining list of studies was cross-checked against the reference lists of relevant studies, and 2 studies (Dozin et al., 2005; Horas, Pelinkovic, Herr, Aigner, & Schnettler, 2003) which were not found in the electronic search were included in the final studies list. At the end, after the application of all inclusion and exclusion criteria, 26 studies (see Table 1.) were selected for this review. Three of these studies (Bentley et al., 2012; Ebert, Fallon, Zheng, Wood, & Ackland, 2012; Knutsen et al., 2007) used the same population of early studies (Bentley et al., 2003; Ebert et al.,

2008; Knutsen et al., 2004). However, they were included since they reported different follow-up periods.

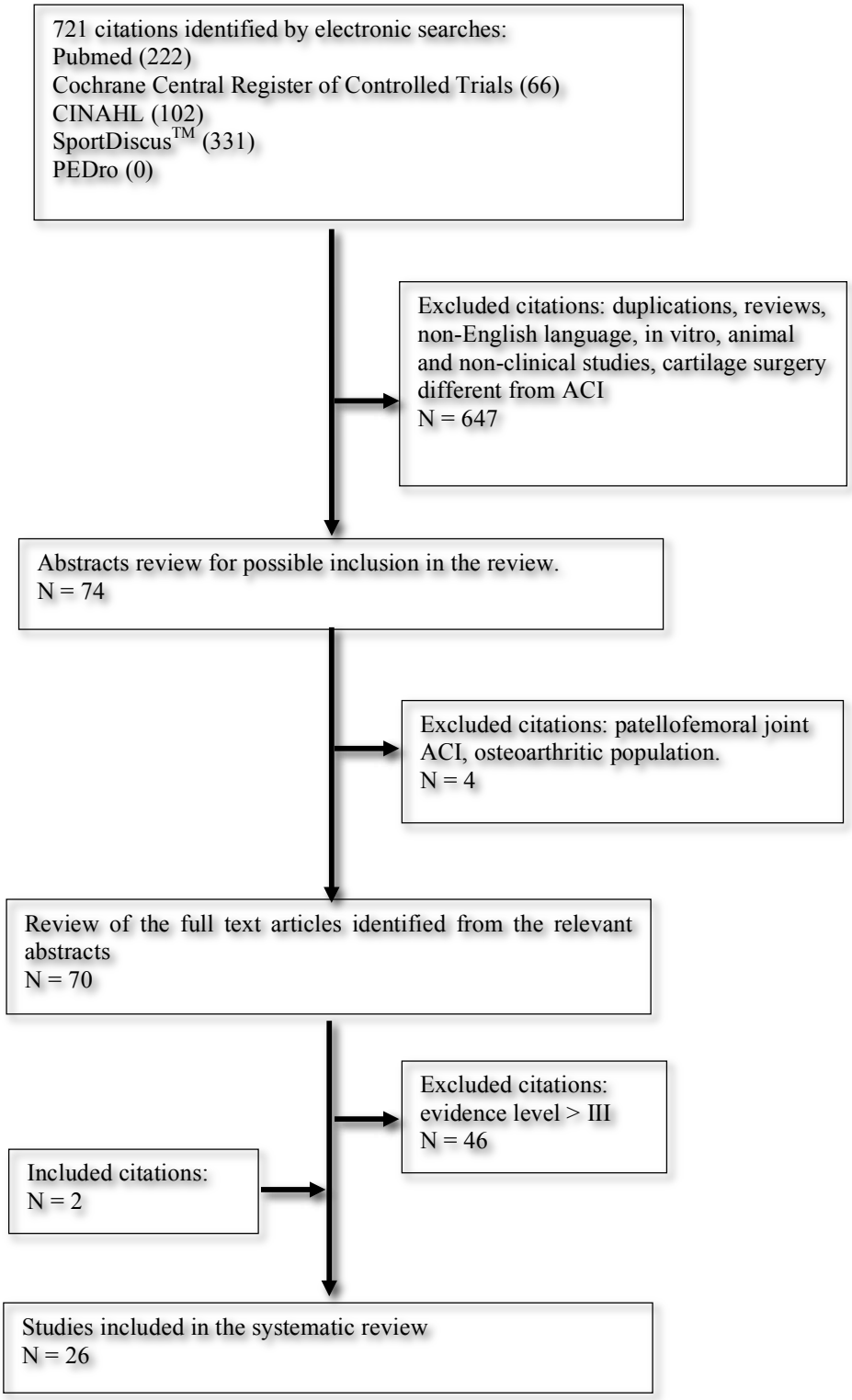

Figure 5 - Flow diagram reporting the selection process of studies

Included Studies Characteristics

There was a wide range of variation in patient demographics across all the twenty-six included studies. The age ranged from 15 to 62 years. The overall number of patients excluding the studies with the same patient cohort was 1595, the number of participants in each study ranged from 19 to 154 patients, and there was a predominance of male gender in all studies. Four studies did not report the gender distribution (Panagopoulos, van Niekerk, & Triantafillopoulos, 2012; Pestka et al., 2012; van Assche et al., 2009; Vanlauwe et al., 2011). In terms of levels of evidence two studies were classified as evidence level III, fourteen studies as level II and ten studies level I (see Table 2.). Fifteen studies were randomized controlled trials, of which nine were categorized as evidence level I studies. Regarding the surgical interventions, eleven studies reported data exclusively from ACI techniques, the remaining studies compared ACI techniques with other techniques, as abrasive techniques, microfracture and/or osteochondral autograft transplantation, and mosaicoplasty. The studies performed predominantly first generation ACI techniques, two studies included second generation ACI, and six studies performed third generation ACI (see Table 2.). Concerning the rehabilitation process, three studies (Ebert et al., 2008; Ebert et al., 2012; Wondrasch, Zak, Welsch, & Marlovits, 2009) distinguished accelerated from delayed weight-bearing after ACI and one study (Della Villa et al., 2010) compared the intensive rehabilitation in athletes to normal rehabilitation in non-athletes. Four studies (Kon et al., 2011; Kreuz et al., 2007; Della Villa et al., 2010 reported data from competitive athletes, in one (Kon et al., 2011) the patients sample was composed only of competitive football players.

Table 2 - Surgical and demographic overview of included studies

Study	Evidence Level	Surgical intervention	Mean Follow-up	Demographics		
				Number of patients	Gender (male / female)	Mean age in years (range)
Bassad, Ishaque, Bachmann, Sturz, & Steinmeyer (2010)	Level I	MACI MF	24 months	40 20	25/15 17/3	33.0 37.5
Bentley et al., (2003)	Level I	Mosaicoplasty ACI	1 years	42 58	27/15 33/25	31.6 (20-48) 30.9 (16-49)
Bentley et al., (2012)	Level II	ACI MF	10 years	58 42	33/25 27/15	30.9 (16-49) 31.6 (20-48)
Cole et al., (2011)	Level II	MF CAIS	24 months	9 20	5/4 14/6	33.1 ± 10.1 32.7 ± 8.8
Della Villa et al., (2010)	Level III	ACI - Hyalograft C (intensive RB athletes) ACI - Hyalograft C (normal RB non-athletes)	5 years	31 34	31/0 34/0	23.5 ± 5.7 25.1 ± 5.8
Dozin et al., (2005)	Level II	ACI Mosaicoplasty	291 days[a] 300 days[a]	22 22	17/5 10/12	29.6 ± 7.3 27.9 ± 8.0
Ebert et al., (2008)	Level II	MACI (accelerated RB) MACI (traditional RB)	3 months	31 31	20/11 20/11	36.9 (21-62) 39.7 (16-60
Ebert et al., (2012)	Level I	MACI (accelerated WB) MACI (normal WB)	5 years	31 32	20/11 21/11	36.8 (21-62) 39.6 (16-63)
Gooding et al., (2006)	Level I	PACI CACI	2 years	33 33	NR NR	30.5 (15-52) 30.5 (16-49)
Horas, Pelinkovic, Herr, Aigner, & Schnettler (2003)	Level II	ACI Osteochondral cylinder	24 months	20 20	8/12 15/5	31.4 (18-42) 35.4 (21-44)
Knutsen et al., (2004)	Level I	ACI MF	2 years	40 40	NR NR	33.3 31.1
Knutsen et al., (2007)	Level I	ACI MF	5 years	40 40	NR NR	33.3 31.1
Kon et al., (2009)	Level II	MF ACI - Hyalograft C	5 years	40 40	27/13 33/7	30.6 29.0
Kon et al. (2011)	Level II	MF (football players) ACI (football players)	7.5 years	20 21	20/0 21/0	26.5 (18-35) 23.7 (16-37)
Kreuz et al., (2007)	Level II	ACI (sports people) ACI (non-sports people)	36 months	69 49	44/25 25/24	35 (18-50) 36.3 (18-50)
Lim et al., (2012)	Level II	MF OAT ACI	5 years	30 22 18	17/13 12/10 10/8	32.9 (30-45) 30.4 (20-39) 25.1 (18-32)
Niemeyer et al., (2010)	Level II	MACI (age > 40 years) MACI (age ≤ 40 years)	24 months	37 37	NR NR	44.76 ± 4.53 31.05 ± 6.14
Panagopoulos et al., (2012)	Level II	PACI or MACI (athletes/soldiers)	37.5 months	19	15/4	32.2 (18-43)
Pestka et al., (2011)	Level III	ACI (after failed MF) ACI	48 months 41 months	28 28	16/12 16/12	34.1 ± 9.0 33.6 ± 10.1
Saris et al., (2009)	Level I	CCI MF	36 months	57 61	35/22 41/20	33.9 ± 8.5 33.9 ± 8.5

Table 2 (cont.)

Study	Evidence Level	Surgical intervention	Mean Follow-up	Demographics		
				Number of patients	Gender (male / female)	Mean age in years (range)
Van Assche et al., (2009)	Level I	ACI MF	2 years	33 34	22/11 24/19	31.0 ± 8.0 31.0 ± 8.0
Vanlauwe et al., (2011)	Level I	CCI (symptoms < 3 years) MF (symptoms < 3 years) CCI (symptoms ≥ 3 years) MF (symptoms ≥ 3 years)	60 months	34 39 17 22	71% male 72% male 47% male 59% male	33.3 (18-50) 33.9 (20-50) 34.2 (19-47) 33.9 (18-50)
Visna et al., (2004)	Level II	ACI Abrasive techniques	12 months	25 25	18/7 16/9	29.5 (18-50) 32.2 (21-50)
Wondrash et al., (2009)	Level I	ACI (accelerated WB) ACI (delayed WB)	104 weeks	16 15	12/4 11/4	28.3 (18-53) 33.0 (18-55)
Zaslav et al., (2008)	Level II	ACI (after failed prior surgery)	48 months	154	106/0	34.5 ± 8.1
Zeifang et al., (2009)	Level II	ACI (periosteal) MACI	24 months	10 11	10/0 6/5	29.1 ± 7.5 29.5 ± 11.0

ACI, autologous chondrocyte implantation; CACI, collagen membrane cover ACI; CAIS, cartilage autograft implantation system; CCI, characterized chondrocyte implantation; MACI, matrix-induced ACI; MF, microfracture; NR, not reported; OAT, osteochondral autograft transplantation; PACI, periosteal cover ACI; RB, rehabilitation; WB, weight bearing.

[a] median

Patient-reported Instruments

The self-reported instruments used in each study at each assessment are described in Table 3. The majority of the studies reported multiple assessments with a mean follow-up of 38.6 months. Four studies (Della Villa et al., 2010; Ebert et al., 2012; Knutsen et al., 2007; Kon et al., 2009; Lim, Bae, Song, Park, & Kim, 2012) reported mean follow-up periods of 5 years, one study (Kon et al., 2011) reported 7.5 years and other 10 years (Bentley et al., 2012). However, the majority of the studies only reported mean assessment time and did not report the minimum and maximum assessment time. Where studies did report the range of timescales about the mean assessment time, a wide range of variation was found (Bentley et al., 2003; Dozin et al., 2005; Lim et al., 2012; Panagopoulos et al., 2012; Pestka et al., 2011). The self-reported physical activity and sports participation instruments utilised in these studies were the TAS, the Modifed Baecke Questionnaire and the Marx ARS. The knee-specific instruments used were Lysholm Knee Function Scale, the IKDC Subjective Form, the KOOS, the Modified CKS, and the Stanmore-Bentley Functional Score; the only

general health questionnaire applied was the SF-36. The main characteristics of each one of these instruments are presented in Table 4. The most utilised instruments were the TAS (13 studies), Lysholm scale (10 studies), IKDC Subjective Form (10 studies) and KOOS (8 studies). Two studies (Kon et al., 2008; Kon et al., 2011) reported the pre-injury TAS. The Lysholm scale was applied together with the IKDC Subjective Form in five studies (Dozin et al., 2005; Niemeyer et al., 2010; Panagopoulos et al., 2012; Visna, Pasa, Cizmar, Hart, & Hoch, 2004; Zeifang et al., 2009), but no studies used the Lysholm scale in conjunction with the KOOS. Three studies applied both the IKDC and KOOS (Cole et al., 2011; Pestka et al., 2011; Wondrasch et al., 2009). Regarding the less used instruments, the Modified CKS was applied in six studies, the SF-36 was used in five studies, Marx ARS and its modified version in two studies, and only one study applied the Modified Baecke Questionnaire (see Table 3.).

Table 3 - Summary of patient-reported instruments used in each study

Study	Assessments time-points (range)	Lysholm	IKDC	KOOS	TAS	Modified CKS	SF-36	Marx ARS	Modified Baecke	Stanmore Bentley
Basad et al., (2010)	Pre-surgery	X			X					
	3 months	X								
	6 months	X			X					
	12 months	X			X					
	18 months	X								
	24 months	X			X					
Bentley et al., (2003)	Pre-surgery					NR				NR
	19 months (12-26)					X				X
Bentley et al., (2012)	Pre-surgery					NR				NR
	Min. 10 years					X				X
Cole et al., (2011)	Pre-surgery		Graph	Graph			Graph			
	6 months		Graph	Graph			Graph			
	12 months		X	X			Graph			
	18 months		Graph	Graph			Graph			
	24 months		X	X			Graph			
Della Villa et al., (2010)	Pre-surgery		X		X					
	12 months		X							
	24 months				X					
	5 years		X		X					
Dozin et al., (2005)	Pre-surgery	X	NR							
	Mosaicoplasty group									
	291 days[a] (0-1339)	X	NR							
	ACI group									
	300 days[a] (0-994)	X	NR							

Table 3 (cont.)

Study	Assessments time-points (range)	Lysholm	IKDC	KOOS	TAS	Modified CKS	SF-36	Marx ARS	Modified Baecke	Stanmore Bentley
Ebert et al., (2008)	Pre-surgery			X			X			
	3 months			X			X			
Ebert et al., (2012)	Pre-surgery			X			X			
	3, 6, 12, 24 months			X			X			
	5 years			X			X			
Gooding et al., (2006)	Pre-surgery					X				
	24 months					X				
Horas et al., (2003)	Pre-surgery	Graph			Graph					
	6,12, 24 months	Graph			Graph					
Knutsen et al., (2004)	Pre-surgery	Graph			NR		Graph			
	12, 24 months	Graph			NR		Graph			
Knutsen et al., (2007)	Pre-surgery	Graph			X		Graph			
	12, 24 months	Graph			NR		Graph			
	5 years	Graph			X		Graph			
Kon et al., (2008)	Pre-injury				X					
	Pre-surgery		X		X					
	24 months		X		X					
	5 years		X		X					
Kon et al., (2011)	Pre-injury				X					
	Pre-surgery		X		X					
	24 months		X		X					
	7.5 years		X		X					

Table 3. (cont.)

Study	Assessments time-points (range)	Lysholm	IKDC	KOOS	TAS	Modified CKS	SF-36	Marx ARS	Modified Baecke	Stanmore Bentley
Kreuz et al., (2007)	Pre-surgery					X				
	6,18, 36 months					X				
Lim et al., (2012)	Pre-surgery	X			X					
	1, 6, 12, 24	X			X					
	36 months	X			X					
	5 years (3-10)									
Niemeyer et al., (2010)	Pre-surgery	X	X		X	X				
	6, 12 months	Graph	X		NR	NR				
	24 months	X	X		X	X				
Panagopoulos et al., (2012)	Pre-surgery	X	X		X					
	3, 6, 12, 36 months	Graph	Graph		Graph					
	37.5 months (36-42)	X	X		X					
Pestka et al., (2011)	Pre-surgery							Xb		
	ACI (failed MF) group									
	48 months (15.1-75.1)		X	X				Xb		
	ACI group									
	41.4 (15.4-83.6)		X	X				Xb		
Saris et al., (2009)	Pre-surgery			Graph						
	6, 12, 24 months			Graph						
	3 years			X						

Table 3. (cont.)

Study	Assessments time-points (range)	Lysholm	IKDC	KOOS	TAS	Modified CKS	SF-36	Marx ARS	Modified Baecke	Stanmore Bentley
Van Assche et al., (2009)	Pre-injury							X		
	Pre-surgery							X		
	12 months							X		
	24 months							X	X	
Vanlauwe et al., (2011)	Pre-surgery			X						
	12, 24 months			Graph						
	36, 48 months			Graph						
	60 months			X						
Visna et al., (2004)	Pre-injury				X					
	Pre-surgery	X	X		X					
	5 months	X	X		NR					
	12 months	X	X		X					
Wondrash et al., (2009)	Pre-surgery		Graph	Graph	Graph					
	4, 12, 24, 52 weeks		Graph	Graph	Graph					
	104 weeks		X	X	X					
Zaslav et al., (2008)	Pre-surgery			X		X				
	6, 12, 24, 36, 48 months			X		X				
Zeifang et al., (2009)	Pre-surgery	X	X		X					
	3, 6 months	NR	NR		X					
	12, 24 months	X	X		X					

ARS, activity rating scale; CKS, Cincinnati Knee Score; IKDC, International Knee Documentation Committee Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; Lysholm, Lysholm Knee Function Scale; SF-36, Short Form-36 Health Survey; Stanmore-Bentley, Stanmore-Bentley Functional Score; NR, not reported; Graph, graphical results.
[a] median; [b] Modified Marx ARS.

Table 4 - Characteristics of the patient-reported instruments

Patient-reported Instruments	Score	Number of items	Subscales or sub-scores	Validated or recommended for ACR
Knee specific				
Modified CKS	0-100	10	Sports activity; change in sports activity, function, ability to participate in sports, symptoms	Recommended (Bartlett et al., 2005)
IKDC Subjective Form	0-100	18	Symptoms, sport activities, function	Validated (Engelhart et al., 2012)
KOOS	0-100	42	Pain, symptoms, function in daily living activities, knee-related quality of life, function in sport and recreation	Validated (Bekkers et al., 2009)
Lysholm	0-100	8	Instability, pain, catching, locking, swelling, stair climb, squat, limp, support	No
Stanmore-Bentley	0-4	4		No
Physical activity scales				
Marx ARS	0-16	4	Running, cutting, decelerating, pivoting	No
Modified Baecke	0-10	10	Household, sport, leisure	No
TAS	0-10	1		No
General health questionnaires				
SF-36	0-100	36	Physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, physical component, scale, mental component scale	Recommended (Bartlett et al., 2005)

ACR, Articular cartilage repair; ARS, activity rating scale; CKS, Cincinnati Knee Score; IKDC, International Knee Documentation Committee Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; Lysholm, Lysholm Knee Function Scale; Baecke, Baecke Questionnaire; SF-36, Short Form-36 Health Survey; Stanmore-Bentley, Stanmore-Bentley Functional Scale.

6. Discussion

This was the first systematic review to specifically evaluate the use of patient-reported activity scoring instruments following ACI from a rehabilitative perspective. Previous reviews have been published for patient-based instruments for the knee in general (Collins et al., 2011; Garratt et al., 2002; Wang et al., 2010; Wright, 2009) and for other specific knee disorders (Alviar et al., 2011; Johnson & Smith, 2001). Recently Chalmers et al. (2013) published a review of activity-related outcomes for articular cartilage repair, but this review was written from a surgical and clinical outcome perspective, rather than rehabilitative and did not focus specifically on ACI.

The first finding in this review was the wide range in the studies demographics in relation to patient numbers (19 to 154), age (15 to 62 years), and postoperative reporting time-points (3 to 83.6 months). Importantly, it was not only the selection of study time-points that varied but also the range in data collection times about those points, which in some instances was up to 5 years (Lim et al., 2012; Pestka et al., 2011). However, the majority of the studies did not report these range values. These inconsistences in reporting are pertinent to rehabilitation as it is a time-based process. It is recommended that researchers should consider reporting the range in postoperative times alongside the mean time for patient-reported outcome evaluations. The main finding from this review was the large degree of heterogeneity between studies in the use of patient-reported instruments to evaluate physical activity and return to sport. This was not only observed in the selection of an individual instrument, but also within the set or group of instruments applied, particularly, the combinations of physical activity scales, knee-specific instruments, and general health questionnaires. This heterogeneity in reporting physical activity does not seem to be related to study demographics or the generation of the ACI technique that is performed. Instrument selection is more likely to be determined by individual researcher or research centre preferences for particular instruments. The use of a particular set of instruments within a centre does allow for intra-centre comparison, but the variation in the selection of physical activity scales and knee-specific instruments between centres makes inter-centre comparisons problematic.

As reported in the results, the most utilised instruments were the TAS, Lysholm Knee Functional Scale, IKDC Subjective Form, and KOOS. The higher prevalence of

TAS is not a surprise, since it is the most widely used activity scoring system for patients with knee disorders (Briggs et al., 2006). The TAS is a single item instrument designed as a score of activity level to complement the Lysholm scale for patients with ligamentous injuries (Lysholm & Gillquist, 1982; Tegner & Lysholm, 1985). Despite generally demonstrating acceptable psychometric parameters (Hambly, 2011b) neither the TAS nor the Lysholm scale have been validated for the cartilage repair population. The TAS scores a person's activity level between 0 to 10 where 0 is "on sick leave/disability" and 10 is "participation in competitive sports such as soccer at a national or international elite level" (Tegner & Lysholm, 1985). Inspite of the possible advantage of retrospective assessment, from a rehabilitation perspective, there are significant limitations in using TAS. This scale does not provide any qualitative information regarding intensity, frequency, or the ability to maintain uncompensated participation at the graded activity level. The other activity rating scales identified within this review were the Modified Baecke Questionnaire, the Marx ARS (Van Assche et al., 2009), and also a Modified Marx ARS (Pestka et al., 2011) which included a lifetime sports assessment (Salzmann et al., 2009). The Modified Baecke (Voorrips et al., 1991) is an adapted version of the physical activity questionnaire of Baecke and coworkers (Baecke et al., 1982) developed for the elderly population. This instrument consists of 10 items, with subscores for "household activities", "sport activities", and "leisure time activities" and "sport activities". The sport activity assessment is based on a single item that, despite taking into account frequency, is very poor in terms of the evaluation of intensity, ranging the intensity from "lying, unloaded" to a maximum of "walking, body movements, cycling, swimming". This reflects the elderly population for which the instrument was developed and does not represent the average age profile of individuals who undergo ACI. The Marx ARS is a 4-item scale developed specifically for knee disorders (Marx et al., 2001). This scale grades "running", "cutting", "decelerating", and "pivoting" separately and does take into account the frequency of participation for each activity. However, all the graded activities are running-related, which means that this instrument is not suitable for evaluating ACI when running is restricted in the early and mid-stages of rehabilitation.

Currently, the only validated instruments for a cartilage repair population are the IKDC Subjective Form (Engelhart et al., 2012) and the KOOS (Bekkers et al., 2009). These instruments have some similar items that could result in a potential overlap, especially as both provide a measure of the overall function and symptoms of knee.

Despite this potential overlap, three studies (Cole et al., 2011; Pestka et al., 2011; Wondrasch et al., 2009) included in this review, applied both instruments together. The IKDC is a knee-specific instrument developed to measure symptoms, function and sports activities in patients who have one or more of a variety of knee conditions (Irrgang et al., 2001). The IKDC Subjective Form is a single-index score consisting of 18 items. However, only one of these items is related to the assessment of sports activities and this represents an important limitation of the IKDC Subjective Form. This limitation may be one of the reasons for why none of the included studies in this review used the IKDC Subjective Form independently. Most of the studies applied the IKDC Subjective form together with the TAS (Della Villa et al., 2010; Kon et al., 2009; Niemeyer et al., 2010; Panagopoulos et al., 2012; Zeifang et al., 2009). The KOOS was developed from the disease-specific Western Ontario and McMaster Universities Osteoarthritis Index (Bellamy et al., 1988). The KOOS consists of 42 items with 5 separately scored subscales, one of these subscales is the "function in sport and recreation", which comprises 5 items (Roos et al., 1998). The KOOS capacity of providing these differentiated subscale scores in addition to the overall score is an advantage in comparison to the IKDC. Although, previous research found that the IKDC Subjective Form provided a better overall measure of symptoms and disabilities that were important to individuals who had undergone articular cartilage repair (Hambly & Griva, 2010). When looking specifically at physical activity and sports participation following ACI, both IKDC and KOOS instruments have limitations, as neither instrument evaluates the frequency, duration and the ability of a person to maintain the intensity of the sports activity without compensations.

The other knee-specific instruments found in this review were the Stanmore-Bentley Functional Rating Score (Bentley et al., 2003; Bentley et al., 2012) and the Modified CKS (Bentley et al., 2003; Bentley et al., 2012; Gooding et al., 2006; Kreuz et al., 2007; Niemeyer et al., 2010). The usefulness of the Stanmore-Bentley Functional Rating Score following ACI is very limited following ACI, since it is a very simplistic functional rating scale based on pain and level of activity. On the other hand, the use of the Modified CKS (also known as the Noyes Knee Rating System) could be useful for ACI since it takes into account the intensity and the weekly frequency of the sports activity. The Modified CKS is composed of 10 items that are used to grade "sports activity", "change in sports activity", "function", "ability to participate in sports", and "symptoms", with a score ranging from 0-100 (Noyes, Barber and Mooar, 1989). The

use of the Modified CKS with the SF-36 has been recommended for preoperative evaluation and postoperative review of all patients undergoing ACI Bartlett et al., 2005). However, this instrument is not currently validated for general cartilage repair or ACI population. Curiously, none of the included studies applied the Modified CKS and the SF-36 together.

7. Conclusion

Participation in physical activities, including sport and exercise, is one of the main reasons that individuals choose to undergo ACI of the knee. It is evident from this review that there is considerable heterogeneity in the selection, timing and reporting of patient-reported activity scoring instruments following ACI, which makes a systematic comparison difficult and bias the interpretation of these outcomes. A key finding from this review was that the instruments currently used to evaluate postoperative outcomes in an articular cartilage repair population do not fulfil the rehabilitative needs in the evaluation of physical activity and sports participation. A suitable instrument should not only identify whether an individual is able to participate in certain physical activities but also the quantity and quality of this participation. In particular, from a rehabilitative perspective, the ability to recognise compensatory functional movement and factors that may indicate incomplete rehabilitation and predispose to further injury are not being elucidated from current patient-reported outcome instruments. Further research is needed in the development and validation of physical activity and sports participation patient-reported instruments suited to the ACI population.

CHAPTER 2: NORMATIVE VALUES FOR THE KOOS IN RECREATIONAL MALE MARATHON RUNNERS

Stratified by Age Group and History of Knee Running-Related Injuries

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1. Abstract

The Knee Injury Osteoarthritis Outcome Score (KOOS) is a widely used patient-reported outcome measure in athletes with knee injury. Despite this wide use, normative reference KOOS values for athletic populations are scarce. The aim of this study was to provide age group and history of injury stratified reference KOOS values for male marathon runners. All participants were registered for the 2014 Porto Marathon, a standard-length marathon race (42.2 km). Before the race, a self-developed questionnaire, which included demographic, training and injury history information, as well the KOOS, was administered to 1250 runners. The 548 male recreational runners included in the analysis were distributed within 3 age groups: 18-34 years old (n=121); 35-54 years old (n=365); and 55-74 years old (n=71). Of all included runners, 57 (≈ 10 %) reported to have had a knee running-related injury (RRI) in the previous month that had stopped their training. Recent history of knee RRI was shown to have a significant negative impact on all KOOS subscales scores. In marathon runners with no history of knee RRI, the KOOS subscales values presented, suggest a non-interaction with age. Furthermore, these values were substantially higher compared to previously published normative population-based KOOS score for the two older age groups. The reference KOOS values presented in this investigation may be useful benchmarks to evaluate patient-reported outcomes in runners with knee injury.

2. Introduction

In the last two decades, patient-reported outcome (PRO) measures have become increasingly important health outcomes both in research (Ahmed et al., 2012; Reeve et al., 2013) and within clinical practice (Black et al., 2015; Brundage et al., 2013; Mokkink et al., 2009). PROs are generically defined as measurements of any aspect of patients' health status that come directly from the patient (Food and Drug Administration, 2006). Typically, these measurements consist at standardised questionnaires designed to measure either patients' perceptions of their general health or in relation to specific diseases or conditions (Guyatt, 1995; Guyatt et al., 1993; Patrick & Deyo, 1989), including those affecting the knee (Garratt et al., 2004). The Knee Injury Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998) is a widely used knee-specific PRO (Collins et al., 2011; Wang et al., 2010) that has shown adequate psychometric properties for multiple rheumatologic (Bekkers et al., 2009; Engelhart et al., 2012; Roos & Lohmander, 2003) and orthopedic conditions (Monticone, Ferrante, Salvaderi, Motta, & Cerri, 2013; Peer & Lane, 2013; Roos & Toksvig-larsen, 2003).

Evolving from the disease-specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al., 1988), the KOOS is a self-administered instrument that grades the perceived symptoms and function of individuals with knee injury, and takes approximately 10 minutes to complete. It consists of 42 items rated on a 5-point Likert scale (0–4) in 5 separately scored subscales: pain; symptoms; activities of daily living (ADL), function in sport and recreation; knee-related quality of life (QOL). Subscale items are summed and transformed to a 0-to-100 scale, where higher scores represent better outcomes (Roos et al., 1998). The use of these individual subscales scores enhances the clinical interpretation and acknowledges the impact of different interventions on different dimensions (Collins et al., 2011). Moreover, the sport related subscale score makes the KOOS suitable for younger and more physically active populations (Roos & Lohmander, 2003). Multiple clinical studies have already used KOOS as a treatment outcome measure in injured athletes (Hoch et al., 2015; Salavati et al., 2011). Although, normative reference KOOS scores for athletic populations are still very limited (Cameron et al., 2013; Frobell et al., 2008; Roi et al., 2015).

Long-distance running, particularly running a marathon has become a worldwide social and fitness phenomenon across all ages (Lepers & Cattagni, 2012) with high profile events, such as the London, Boston and New York marathons, each attracting upwards of 30 000 participants, most of them recreational runners (Burfoot, 2007). This growth in participation has been partially driven by the increased public awareness of the short and long-term health benefits related to long-distance running (Day & Thompson, 2010; Drysdale, Collins, Walters, Bird, & Hinkley, 2007; Sarna, Sahi, Koskenvuo, & Kaprio, 2008; Williams, 2009). However, running-related injury (RRI) of the lower extremities, particularly affecting the knee, is a frequent occurrence in long-distance running (van Gent et al., 2007). A substantial number of these injuries occur during training for a marathon race (Fredericson & Misra, 2007; van Mechelen, 1992).

Despite the growing numbers of recreational marathon runners and the substantial incidence of knee RRI among them, the runner's perception of the degree of dysfunction, pain or other knee symptoms has not been evaluated using the KOOS or with any other knee-specific PRO. Therefore, the aim of this study is to provide normative reference values for the KOOS in a population of recreational marathon runners, which account for differences in age and the history of knee RRI.

3. Methods

Design and Setting

The present study was conducted prior to a marathon race in order to establish KOOS normative values for a population of recreational marathon runners. A cross-sectional analysis was performed to evaluate differences in KOOS scores between age groups and between runners with and without recent history of knee RRI. The KOOS scores of our sample of runners were also compared with previously published KOOS reference scores for matching age groups (Cameron et al., 2013; Paradowski, Bergman, Sunden-Lundius, Lohmander, & Roos, 2006). This study was approved by the Ethics Committee at the School of Sport and Exercise Sciences, University of Kent.

Participants

All participants were registered for the 2014 Porto Marathon, a standard-length marathon race (42.2 km) held in Porto city, Portugal. Participants were recruited during the 2-days pre-race registration period at the organization site. Within that period, 1250 questionnaires (50 % of 2013 race finishers) were administered in a randomized manner to the runners who met the following inclusion criteria: (1) recreational/amateur runner (2) resident in the country. The runners who received the questionnaire were informed about the aims of the study and were invited to participate by the research staff present at the organisation site. The runners who decided to participate were then invited to a research stand at the marathon exhibition area, which was specifically prepared to provide the adequate conditions for the runners to complete the informed consent and the questionnaire.

Study Questionnaire

The questionnaire content was based on previous research on RRI (Chang et al., 2012; Hespanhol Junior, Pena Costa, & Lopes, 2013; Van Middelkoop et al., 2008a). The questions included: general demographics; marathon running experience; training history; recent history of RRI; and previous knee surgeries. The administration of the KOOS was the last part of the questionnaire. The training history questions comprised the average weekly run frequency, duration, distance and pace in the previous month. The RRI definition used in previous investigations (Lun, Meeuwisse, Stergiou, & Stefanyshyn, 2004; Macera et al., 1989; Van Middelkoop et al., 2008a) was adapted to construct a more direct question to characterise RRI, as follows: “During the last month have you had a running-related injury that has stopped you running?”. If yes, participants had to answer where from choosing one or more of the following options: “knee”; “foot and/or ankle”; “leg and/or thigh muscles”, “lower back”; and “other”. Participants who reported to have had knee RRI were then asked to discriminate the type of knee injury, choosing between: “ligaments”; “meniscus”; “cartilage”, “other”. All questions were mandatory and multiple-choice style.

Statistics

Data distribution was checked for normality and skewness in all variables. Normally distributed variables are presented in mean and standard deviation. In demographic and training variables independent samples t-tests and Mann-Whitney tests were applied to check the differences between runners who reported knee RRI and those who did not report knee RRI. Normative descriptive values for the KOOS subscales and overall scores were calculated by age groups and history of knee injury. Due to the non-normal distribution of the KOOS subscales scores, the 95% confidence intervals, median, minimum, maximum, interquartile range (IQR) and ceiling effect were also presented for these variables. The highest KOOS subscales and overall scores for each age group were considered as the ceiling score (Roos & Toksvig-Larsen, 2003). The internal consistency of the KOOS scores for each age group was tested using the Cronbach's alpha level. The Mann-Whitney test was applied to assess differences in KOOS scores between runners of the same age group who reported and those who did not report knee RRI. The Kruskal-Wallis test was used to compare the KOOS scores between different age groups in runners without knee injury. Subsequently, pairwise comparisons between age groups were performed using the Dunn's (1964) procedure with a Bonferonni correction for multiple comparisons. The Welch t-test was applied to compare the KOOS subscales scores in our study with previously published KOOS normative scores for similar age groups (Cameron et al., 2013; Paradowski et al., 2006). This test assumes unequal variance and has been recommend to compare measures of central tendency of 2 populations based on samples of unrelated data (Ruxton, 2006). Moreover, it has been described as robust to variations in normality, especially with large samples (Cameron et al., 2013). All analyses were completed using the Statistical Package for the Social Sciences, version 22 for Mac OS X (SPSS Inc., Chicago, IL, USA) with a significance level set at 0.05. Cohen's d effect size was calculated for the t-tests with G*Power software (version 3.1.9.2 for Mac OS X, Universität Düsseldorf, Germany).

4. Results

A flow chart summarising the participant selection is presented in Figure 6. Female runners were not included in this study due to the relatively low number of received questionnaires (n=72), which would limit age group stratification. The age groups range was established in accordance with previous comparable research (Paradowsky et al., 2006). Among the 548 male runners (42.9 ± 10.3 years old) included in the study, 121 (22 %) were within the 18-34 years' age group, 356 (65 %) within the 35-54 years' age group and 71 (13 %) within the oldest age group considered, 55-74 years. Of all included runners, 57 (10 %) reported to have had a recent knee RRI and 121 (22 %) a RRI affecting other areas. Table 4 shows the characteristics of the included runners stratified by history of knee RRI. The most affected structure in runners who reported knee RRI were the ligaments (47 %) and cartilage (46 %). From these, 21% reported previous knee surgery. Knee RRI shown to be associated with lower training pace ($t(546)=-2.410$, $P=0.016$, $d=2.4$). The mean pace difference between knee RRI groups was 0.3 (95 % CI, 0.05 to 0.58) min mile^{-1}. Although, no differences were observed in any other training variable or in marathon running experience.

Table 5 summarises the KOOS values stratified by age group and history of knee RRI. Among all age groups, the KOOS subscales showed an internal consistency ranging between acceptable and excellent ($\alpha=0.73$-0.95). The highest proportion of ceiling effects was observed in runners who did not report knee RRI. Runners who reported knee RRI showed significantly lower scores in all KOOS subscales among all age groups ($P<0.001$) (Table 6.). The age groups comparison between runners without knee RRI, revealed only significant differences for KOOS Symptoms ($X^2(2)=8.379$, $P=0.015$) and KOOS QOL ($X^2(2)=6.531$, $P=0.038$) subscales scores (Table 7). In both subscales the post hoc pairwise comparison analysis showed no differences between the two oldest age groups ($P\geq0.674$). The comparison of KOOS subscales scores from the current study with previously published age group matched normative data (Cameron et al., 2013; Paradowski et al., 2006) is presented in Tables 8 and 9. For the 18-34 years' age group, the KOOS subscales scores in the current study, with the exception of the Sports and Recreation Function subscale ($t(79)=2.407$, $P=0.018$, $d=2.4$), were not

different from the general normative values published by Paradowski et al., (2006). Although, these scores were significantly lower (P≤0.005) when compared with the normative values reported for a young athletic population (Cameron et al., 2013). For the older age groups, the majority of the KOOS subscales values observed in the current study were significantly higher than the general population reference values (Paradowski et al., 2006). The exceptions were the Pain subscale score for the 35 to 54 years old age group (P=0.061) and the Symptoms subscale score in the 55 to 74 years old (P=0.170) age groups.

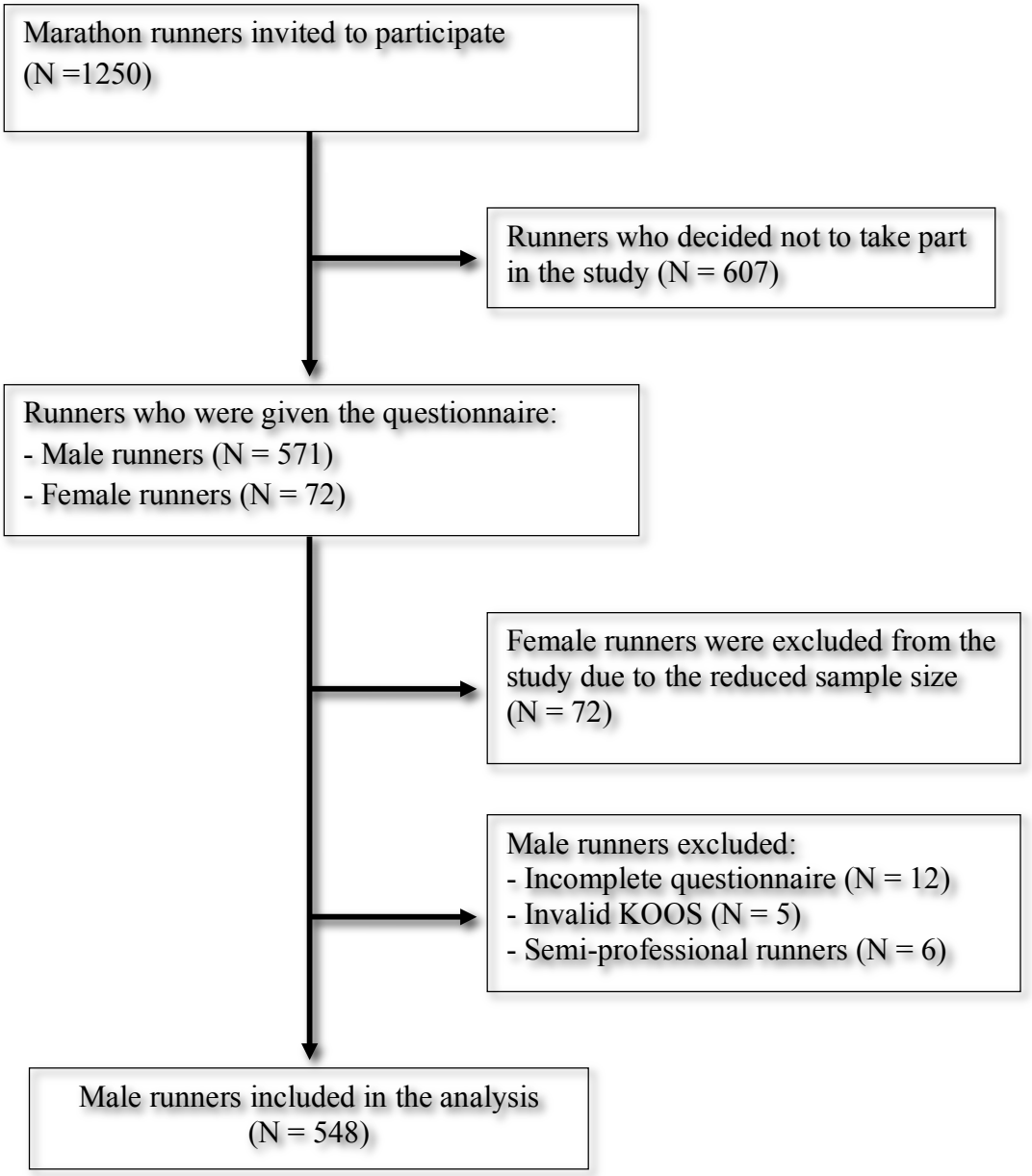

Figure 6 – Marathon runners selection flowchart

Table 5 - Description of participants stratified by history of knee running-related injury

		Reported Knee RRI		
	All runners (N=548)	**No (n=491)**	**Yes (n=57)**	***P***
Age (years), mean ± SD	42.9 ± 10.3	42.9 ± 10.1	43.1 ± 12.4	0.923
Age-groups distribution				
18-34, n (%)	121 (22.0)	104 (21.2)	17 (29.8)	
35-54, n (%)	356 (65.0)	328 (66.8)	28 (49.1)	
55-75, n (%)	71 (13.0)	29 (12.0)	12 (21.1)	
Body mass (kg), mean ± SD	71.5 ± 8.2	71.4 ± 8.2	72.3 ± 8.3	0.486
Height (m), mean ± SD	1.75 ± 0.1	1.76 ± 0.1	1.75 ± 0.1	0.345
BMI (kg/m^2), mean ± SD	23.2 ± 2.2	23.3 ± 2.2	23.7 ± 2.2	0.091
Weekly training				
Frequency (days), mean ± SD	4 ± 1	4 ± 1	4 ± 1	0.066
Hours (h), mean ± SD	6.0 ± 2.2	6.0 ± 2.2	5.6 ± 2.3	0.184
Distance (miles), mean ± SD	35.7 ± 12.4	36.0 ± 12.5	33.0 ± 11.5	0.068
Pace ($min\ mile^{-1}$), mean ± SD	8.7 ± 0.9	8.7 ± 1.0	9.0 ± 0.9	0.016
Marathon running experience				
First timers, n (%)	205 (37.5)	186 (37.9)	19 (33.3)	
Non first-timers, n (%)	343 (62.5)	305 (62.1)	38 (66.7)	
No. of races, median (IQR)	3.0 (4.0)	3.0 (4.0)	3.5 (6.3)	0.129
Type of knee injury				
Ligaments, n (%)			26 (45.6)	
Meniscus, n (%)			4 (7)	
Cartilage, n (%)			27(47.4)	
Other, n (%)			0 (0)	
Previous knee surgeries				
No, n (%)	490 (89.4)	445 (90.6)	45 (78.9)	
Yes, n (%)	68 (10.6)	46 (9.4)	12 (21.1)	

BMI, body mass índex; IQR, interquartile range; RRI, running-related injury.

Table 6 - KOOS outcomes stratified by age group and history of knee running related injury

										Ceiling Effect	
		n	Mean + SD	Median	95% CI	*P*	Min	Max	IQR	n	%
KOOS Pain											
18-34 years	No Injury	104	92.2 ± 10.1	94.4	90.2-94.1	< 0.001	33.3	100.0	11.1	28	26.9
	Injury	17	76.8 ± 14.0	80.6	69.6-84.0		47.2	94.4	18.1	1	5.9
35-54 years	No Injury	328	91.3 ± 12.6	97.2	90.0-92.7	< 0.001	36.1	100.0	11.1	138	42.1
	Injury	28	66.4 ± 15.6	66.7	60.3-72.4		41.7	100.0	26.8	2	7.1
55-74 years	No Injury	59	93.7 ± 9.3	97.2	91.3-96.1	< 0.001	61.1	100.0	8.3	22	37.3
	Injury	12	70.0 ± 15.4	65.3	60.1-69.7		47.2	100	10.4	2	16.7
KOOS Symptoms											
18-34 years	No Injury	104	88.4 ± 9.9	89.3	86.5-90.3	< 0.001	60.7	100.0	14.3	21	20.2
	Injury	17	76.6 ± 10.4	75.0	71.4-82.0		64.3	92.9	21.5	2	11.8
35-54 years	No Injury	328	90.6 ± 11.3	92.9	89.3-91.8	< 0.001	39.3	100.0	14.3	102	31.1
	Injury	28	87.9 ± 13.5	91	67.5-79.2		42.3	96.4	26.8	2	7.1
55-74 years	No Injury	59	91.5 ± 9.2	92.9	89.2-94.0	< 0.001	67.9	100.0	14.3	22	37.3
	Injury	12	70.5 ± 15.1	71.4	60.9-80.1		50.0	92.9	26.7	2	16.7
KOOS ADL											
18-34 years	No Injury	104	96.2 ± 5.4	98.5	95.2-97.3	< 0.001	75.0	100.0	5.9	43	41.3
	Injury	17	77.7 ± 17.0	79.4	68.9-86.3		32.4	98.5	19.1	1	5.9
35-54 years	No Injury	328	94.7 ± 9.2	98.5	93.8-95.8	< 0.001	47.1	100.0	5.9	155	47.3
	Injury	28	75.5 ± 18.2	78.7	68.4-82.5		42.6	97.1	30.2	2	7.1
55-74 years	No Injury	59	94.6 ± 8.3	98.5	92.4-96.7	< 0.001	70.6	100.0	8.8	27	45.8
	Injury	12	73.7 ± 17.3	75.0	62.6-84.6		45.6	100.0	16.9	2	16.7

Table 6 (cont.)

		n	Mean + SD	Median	95% CI	*P*	Min	Max	IQR	Ceiling Effect	
										n	%
KOOS Sports and Recreation Function											
18-34 years	No Injury	104	92.1 ± 11.4	100.0	89.9-94.4	< 0.001	50.0	100.0	13.8	54	51.9
	Injury	17	65.3 ± 16.6	60.0	56.7-73.8		20.0	85.0	22.5	3	17.6
35-54 years	No Injury	328	88.8 ± 14.6	95.0	87.2-90.4	< 0.001	30.0	100.0	20.0	147	44.8
	Injury	28	60.2 ± 19.6	55.0	52.5-67.8		30.0	100.0	23.8	2	7.1
55-74 years	No Injury	59	89.6 ± 12.7	95.0	86.3-92.9	< 0.001	50.0	100.0	20.0	25	42.4
	Injury	12	53.8 ± 21.1	55.0	40.3-67.2		15.0	80.0	42.5	1	8.3
KOOS Knee-Related QOL											
18-34 years	No Injury	104	88.4 ± 14.5	93.8	84.6-90.2	< 0.001	50.0	100.0	25.0	46	44.2
	Injury	17	68.0 ± 18.3	75.0	58.6-77.5		37.5	93.8	31.3	2	11.8
35-54 years	No Injury	328	90.0 ± 14.8	100.0	88.4-91.6	< 0.001	31.3	100.0	18.7	177	54.0
	Injury	28	58.2 ± 20.0	56.3	50.4-66.0		25.0	93.8	25.0	4	14.3
55-74 years	No Injury	59	93.6 ± 10.0	100.0	91.0-96.3	< 0.001	62.5	100.0	12.5	34	57.6
	Injury	12	67.7 ± 20.8	62.5	54.5-90.0		43.8	100.0	37.5	2	16.7

Table 6 (cont.)

		n	Mean + SD	Median	95% CI	*P*	Min	Max	IQR	Ceiling Effect	
										n	%
KOOS Overall											
18-34 years	No Injury	104	91.2 ± 7.8	93.2	89.7-92.8	< 0.001	62.9	100.0	11.8	11	10.6
	Injury	17	72.9 ± 10.4	73.0	67.5-78.2		49.9	87.5	15.5	1	5.9
35-54 years	No Injury	328	91.1 ± 11.1	95.4	88.9-92.3	< 0.001	42.1	100.0	12.2	61	18.6
	Injury	28	66.7 ± 14.5	67.6	61.1-72.3		38.3	96.4	23.2	2	7.1
55-74 years	No Injury	59	92.6 ± 8.3	94.6	90.4-94.8	< 0.001	66.1	100.0	9.9	12	20.3
	Injury	12	67.1 ± 16.2	64.5	56.8-77.4		48.2	94.6	26.2	1	8.3

ADL , activities of daily life; CI, confidence interval; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; Max, maximum; Min, minimum; QOL, quality of live.

Table 7 - Comparison of KOOS outcomes between age groups of runners without knee injury

	Age-groups			*P* Values			
	18-34 y.o. (n = 104)	**35-54 y.o. (n = 328)**	**55-74 y.o. (n = 59)**	**Overall**	**18-34 vs. 35-54 years**	**18-34 vs. 55-74 years**	**35-54 vs. 55-74 years**
KOOS Pain							
Mean ± SD	92.2 ± 10.1	91.3 ± 12.6	93.7 ± 9.3	0.356	0.258	0.150	0.574
Median	94.4	97.2	97.2				
IQR	11.1	11.1	8.3				
95% CI	90.2-94.1	90.0-92.7	91.3-96.1				
KOOS Symptoms							
Mean ± SD	88.4 ± 9.9	90.6 ± 11.3	91.5 ± 9.2	0.015	0.019	0.074	1.000
Median	89.3	92.9	92.9				
IQR	14.3	14.3	14.3				
95% CI	86.5-90.3	89.3-91.8	89.2-94.0				
KOOS ADL							
Mean ± SD	96.2 ± 5.4	94.7 ± 9.2	94.6 ± 8.3	0.861	0.636	0.905	0.718
Median	98.5	98.5	98.5				
IQR	5.9	5.9	8.8				
95% CI	95.2-97.3	93.8-95.8	92.4-96.7				
KOOS Sports and Recreation Function							
Mean ± SD	92.1 ± 11.4	88.8 ± 14.6	89.6 ± 12.7	0.161	0.062	0.172	0.986
Median	100	95	95				
IQR	13.8	20	20				
95% CI	89.9-94.4	87.2-90.4	86.3-92.9				

Table 7 (cont.)

	Age-groups			*P* Values			
	18-34 years (n = 104)	**35-54 years (n = 328)**	**55-74 years (n = 59)**	**Overall**	**18-34 vs. 35-54 years**	**18-34 vs. 55-74 years**	**35-54 vs. 55-74 years**
KOOS QOL							
Mean ± SD	88.4 ± 14.5	90.0 ± 14.8	93.6 ± 10.0	0.038	0.145	0.047	0.674
Median	93.8	100	100				
IQR	25	25	12.5				
95% CI	84.6-90.2	88.4-91.6	91.0-96.3				
KOOS Overall							
Mean ± SD	91.2 ± 7.8	91.1 ± 11.1	92.6 ± 8.3	0.235	0.129	0.126	0.734
Median	93.2	95.4	94.6				
IQR	11.8	12.2	9.9				
95% CI	89.7-92.8	88.9-92.3	90.4-94.8				

ADL, activities of daily life; CI, confidence interval; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life.

Table 8 - Comparison of KOOS outcomes in the current study with previously published comparable normative values for a non-injured male population in 18-34 years old age group

	Age Groups			*P* Values	
	Current Study (n = 104)	**Cameron et al., (2013) (n = 832)**	**Paradowsky et al., (2006) (n = 60)**	**Current Study vs. Cameron et al., (2013)**	**Current Study vs Paradowsky et al., (2006)**
KOOS Pain					
Mean ± SD	92.2 ± 10.1	97.5 ± 6.3	93.7 ± 9.3	< 0.001	0.336
Median	94.4	100.0	97.2		
95% CI	90.2-94.1	97.0-97.9	89.8-95.6		
KOOS Symptoms					
Mean ± SD	88.4 ± 9.9	94.0 ± 8.0	87.2 ± 13.9	< 0.001	0.173
Median	89.3	96.4	92.9		
95% CI	86.5-90.3	93.4-94.5	83.6-90.8		
KOOS ADL					
Mean ± SD	96.2 ± 5.4	98.9 ± 3.8	94.2 ± 10.0	< 0.001	0.155
Median	98.5	100	100		
95% CI	95.2-97.3	98.6-99.1	91.6-96.7		
KOOS Sports and Recreation Function					
Mean ± SD	92.1 ± 11.4	94.8 ± 10.4	85.1 ± 20.8	0.002	0.018
Median	93.8	100	92.5		
95% CI	89.9-94.4	94.1-95.5	79.7-90.5		
KOOS QOL					
Mean ± SD	88.4 ± 14.5	92.6 ± 11.2	85.3 ± 19.2	0.005	0.280
Median	93.3	100	93.8		
95% CI	84.6-90.2	91.9-93.4	80.3-90.3		

ADL, activities of daily life, CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life.

Table 9 - Comparison of KOOS outcomes in the current study with previously published comparable normative values for a non-injured male population in 35-54 and 55-74 years old age groups

	35-54 years Age Group			55-74 years Age Group		
	Current Study (n = 328)	**Paradowsky et al., (2006) (n = 78)**	***P***	**Current Study (n = 59)**	**Paradowsky et al., (2006) (n = 88)**	***P***
KOOS Pain						
Mean ± SD	91.3 ± 12.6	87.4 ± 17.9	0.071	93.7 ± 9.3	87.7 ± 17.4	0.007
Median	97.2	97.2		97.2	97.2	
95% CI	90.0-92.7	83.4-91.5		91.3-96.1	84.0-91.4	
KOOS Symptoms						
Mean ± SD	90.6 ± 11.3	86.5 ± 16.7	0.042	91.5 ± 9.2	88.4 ± 17.3	0.160
Median	92.9	92.9		92.9	96.4	
95% CI	89.3-91.8	82.7-90.2		89.2-94.0	84.8-92.1	
KOOS ADL						
Mean ± SD	94.7 ± 9.2	89.1 ± 17.6	0.007	94.6 ± 8.3	86.3 ± 18.8	< 0.001
Median	98.5	100		98.5	97.1	
95% CI	93.8-95.8	85.1-93.1		92.4-96.7	82.3-90.3	
KOOS Sports and Recreation Function						
Mean ± SD	88.8 ± 14.6	76.0 ± 29.5	< 0.001	89.6 ± 12.7	72.6 ± 29.9	< 0.001
Median	95	87.5		95	80	
95% CI	87.2-90.4	69.2-82.7		86.3-92.9	66.2-78.9	
KOOS QOL						
Mean ± SD	90.0 ± 14.8	77.7 ± 25.4	< 0.001	93.6 ± 10.0	78.9 ± 25.4	< 0.001
Median	100	87.5		100	87.5	
95% CI	88.4-91.6	72.0-83.5		91.0-96.3	73.5-84.3	

ADL, activities of daily life; CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life.

5. Discussion

To our knowledge this study was the first to evaluate knee symptoms and dysfunction in recreational marathon runners using the KOOS. Among the available PRO measures, the KOOS was selected due to the large body of evidence supporting its use in multiple clinical and research settings (Collins et al., 2011; Garratt et al., 2004; Wang et al., 2010), including following ACI, as reported in the systematic review conducted in Part 1, Study 2. However, despite of KOOS widespread use, there is a paucity of normative reference values for this instrument, especially for athletic populations (Cameron et al., 2013). The only reference KOOS subscales scores available are for amateur football players (Frobell et al., 2008), young individuals entering the military academy (Cameron et al., 2013), and for downhill runners (Roi et al., 2015). This main aim of this study was to provide normative reference values for the KOOS subscales scores in a population of recreational male marathon runners, which accounted for age groups and history of knee RRI.

The incidence of knee RRI found in our results was approximately 10 %, which aligns within the incidence described in the literature. Previous epidemiological studies conducted with marathon runners described incidence rates of knee RRI preceding a race, ranging between 5% and 32% (Van Middelkoop et al., 2008a; Chang et al., 2012; Maughan & Miller, 1983; Kretsch et a1., 1983). This variability on the reported incidence rate may arise from the methodological heterogeneity between studies (van Gent et al., 2007), particularly in the definition of RRI and the recall period considered. In the current study, RRI was defined as a problem severe enough not to reduce training but instead, to interrupt it, which we believe is a clearer definition and also provides a more insightful reflection of the impact of the injury on the individual runner. The recall period considered was relatively short, 1 month. Thus, making the RRI question more objective, facilitating runners' answer. Relatively similar RRI definitions (Hespanhol Junior et al., 2013; Maughan & Miller, 1983) and analogous recall periods (Roi et al., 2015; Van Middlekoop et al., 2008a) have been used in different running studies.

In terms of the KOOS scores, our results showed that independently of the age group, runners who have reported knee RRI had significantly lower scores in all

subscales comparatively to their non-injured counterparts. Similar trends were observed in the previous studies conducted in physically active populations (Cameron et al., 2013; Frobell et al., 2008; Roi et al., 2015). However, the knee injury definition, the recall period, and the physical activity profile varied substantially among these studies. Cameron et al., (2015) in a study conducted with young males and females entering the military service, uniquely considered knee injuries affecting the ligaments and the recall period was lifetime. A similar recall period was used in a study with Swedish football players (Frobell et al., 2008); though detailed knee injury information, including type categorisation, as well as diagnostic assessment and treatment were collected. More recently, a research conducted with downhill runners (Roi et al., 2015) used a 1 month injury recall period but the defining criteria of knee injury was not described.

In the present study, the magnitude of the KOOS scores difference between runners who reported knee RRI and those who did not (Table 6), might not only reflect the severity of the injury but also ceiling effects observed in non-injured runners. Interestingly, ceiling effects were not only prevalent in the 18-34 age group, but also among the older age groups. A similar impact of ceiling effects has been also reported in young athletic individuals without history of knee ligaments injury (Cameron et al., 2013). This finding might be explained by the fact that running a marathon requires a high physical and mental aptitude and fitness (Midgley, McNaughton, & Jones, 2007). It is likely that numerous runners without knee injury may present very high KOOS values, regardless of their age.

In the current study, the age group intervals were primarily defined to allow KOOS subscales score matched comparisons with previously published population-based reference values (Paradowsky et al., 2006). To evaluate the potential effect of age on KOOS scores an inter age group comparison analysis was also performed. The results of this analysis have shown that age seems to be unrelated with KOOS scores in male marathon runners without knee injury, particularly in individuals older than 34 years old. This finding is in line with the previously mentioned studies conducted with athletic populations (Frobell et al., 2008; Roi et al., 2015). Although, it is contrary to what has been described for the general population. The only population-based normative values available for the KOOS is from a Swedish study conducted by Paradowsky et al., (2006), which consisted of a random sample, stratified by age and gender, selected through regional population public records. For the 18-34 age group,

our KOOS subscales scores and this population-based study were not different, with the exception of the Sports and Recreation Function subscale. This subscale score was significantly higher in our study, which can be explained by the athletic nature of our sample. However, for this same age group all KOOS scores were found to be significantly lower comparatively to the normative values reported by Cameron et al., (2013). The difference in the sports related score certainly reflect the heterogeneity in physical activity profile between samples and possibly the mean age gap (30.5 ± 3.5 vs. 18.8 ± 0.9 years). Although, as mentioned, within the same athletic population age might not be a relevant determinant of KOOS as it is for the general population. For the older age groups, 35-54 and 55-74 years, our results demonstrate that marathon runners without knee injury are likely to have higher KOOS scores than the general population. This finding highlights that the rehabilitation goals for a runner, and possibly to other athletic populations, must not be guided by the KOOS scores for the general population. Similarly, reporting of outcomes from injury surgery and/or rehabilitation should recognise that successful outcome for a runner is not achievement of the KOOS scores equivalent to the general population, especially for the older age groups. The difference observed between our results and the general population KOOS normative scores for the older age groups, is possibly because the physical activity level and the history of knee injury were not considered by Paradowsky et al., (2006). Therefore, their sample physical activity profile was unknown and it probably included knee injured individuals, which might explain the lower scores.

The reference KOOS subscales scores for male marathon runners, stratified by age and history of knee RRI, provided by the current study may be a valuable asset for clinicians and sport rehabilitation professionals when evaluating perceived knee symptoms and function in long-distance runners. Specifically, knowing population specific KOOS subscale scores may allow the setting and evaluation of self-reported rehabilitation goals for male marathon runners with knee injury.

This investigation has limitations that should be acknowledged when interpreting the results. The first limitation is a potential sample selection bias. Despite the random distribution of the questionnaires among the registered runners and the relatively high response rate in males (≈ 70 %), it is not possible to guarantee that the inclusion of runners who were not selected to participate, as well the ones who were selected but did not choose to participate, would not have an impact in the results.

Second, the intrinsic bias associated with PRO measures can also be considered a limitation (Marquis, Arnould, Acquadro, & Roberts, 2006). In this study, we did not collect any objective clinical parameters to correlate with KOOS; although KOOS has previously shown adequate psychometric properties for several knee injuries (Collins et al., 2011) and has been used as a treatment outcome with athletic populations (Hoch et al., 2015; Salavati et al., 2011). The injury recall period being self-reported and retrospective, not assessing a second and wider injury recall period (i.e., 6 months), as well the re-injury rate and the duration of the training interruption due to RRI, are also limitations of this investigation. Future research is needed to confirm the findings of the current study, as well to provide reference KOOS scores for female long-distance runners. Furthermore, the conduct of longitudinal studies assessing the impact of a marathon race on KOOS scores would also be of a great value.

6. Conclusion

This is the first study to have present reference KOOS subscales scores from a large sample of male marathon runners, stratified by age and history of knee RRI. In this population, regardless of the age, history of knee RRI was shown to have a significant negative impact on all KOOS subscales scores. For runners without knee injury, age seems to be unrelated with KOOS and the scores presented were substantially higher than the previously published normative population-based values. The reference KOOS subscales scores provided in the current study may allow comparisons with other athletic populations, particularly across a wide age range. Furthermore, and possibly more relevant, these scores may be used as benchmarks by clinicians and sport rehabilitation professionals to measure treatment outcomes in long-distance runners with knee injury.

PART II

SINGLE-LEG CYCLING EXERCISE TESTING

CHAPTER 1: RELIABILITY OF SELF-PACED SINGLE-LEG CYCLING EXERCISE TESTING

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1. Abstract

The self-paced test (SPT) concept of short duration, closed-loop design and rating of perceived exertion (RPE) orientated intensities could be advantageous for clinical single-leg cycling (SLC) exercise testing, particularly in athletes following knee surgery and/or injury. Given that the SPT concept has never been used in SLC, the purpose of this study was to investigate the reliability of a SPT protocol for SLC exercise testing. Ten male recreationally active participants (age 27 ± 6 years old, stature 1.75 ± 0.07 m, body mass 77 ± 14 kg) with no previous experience of SLC, took part in this study. Participants repeated a SLC maximal SPT protocol in 3 separate sessions. The SPT protocol consisted of 5x2 min stages, where for each stage, participants were asked to vary their power output to match incrementally ordered RPE levels (11, 13, 15, 17 and 20). No significant differences between sessions were found in peak power output (PPO), peak oxygen uptake (VO_{2peak}), peak heart rate (HR_{peak}), peak respiratory exchange ratio (RER_{peak}), peak minute ventilation (VE_{peak}) and 1 min post-test blood lactate ($BL_{1\text{-}min}$). With the exception of $BL_{1\text{-}min}$, all other variables showed good relative reliability (ICC > 0.75). Small standard error of measurements, residuals homoscedascity and relatively narrow 95 % Bland and Altman's limits of agreement were also observed. Furthermore, session was not a main effect of power output and oxygen uptake throughout the tests. This investigation demonstrates a 5x2 min SPT protocol may elicit reliable peak cardiorespiratory and metabolic responses in SLC exercise testing.

2. Introduction

Traumatic knee injuries that require surgery and/or extended periods of rehabilitation, such as ligament tears, are relatively common in contact sports (Kujala et al., 1995; Loes et al., 2000; Majewski et al., 2006; Ristolainen et al., 2010). These injuries often require a substantial reduction in physical activity and prolonged training cessation (Mujika & Padilla, 2003). For example, following an anterior cruciate ligament (ACL) tear the return to light sporting activities such as running, may occur only 2–3 months after surgery (Kvist, 2004; van Grinsven et al., 2010). Other knee surgeries, such as posterior cruciate ligament (PCL) reconstruction or cartilage repair procedures have an even more delayed return to sport (Della Villa et al., 2010; Fanelli, 2008; Mithoefer et al., 2012). Maintained training cessation or insufficient training stimulus results in partial or complete loss of previously acquired physiological and performance adaptations (Coyle, 1984; Hawley & Burke, 1998). This gradual deconditioning process is often termed as detraining (Mujika & Padilla, 2000a; Mujika & Padilla, 2000b). In endurance athletes, cardiorespiratory detraining is particularly rapid (Mujika & Padilla, 2003). Multiple studies have shown that maximal oxygen uptake (VO_{2max}) may decline by 6 to 20 % when training cessation is longer than 3 weeks (Coyle et al., 1984; Ghosh, Paliwal, Sam, & Ahuja, 1987; Mankowitz, Seipa, Semenkovich, Daughert, & Schonfeld, 1992; Martin et al., 1986).

Following knee surgery and throughout rehabilitation where conventional bilateral exercise is contraindicated, single-leg cycling (SLC) exercise testing has been used to assess the cardiorespiratory deconditioning and reconditioning (Olivier et al., 2008; Olivier et al., 2010). This exercise modality has also been utilised in other clinical populations, including chronic obstructive pulmonary disease patients (COPD) (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006) and lower-limb amputees (Wezenberg et al., 2012). SLC exercise testing has been only performed through conventional incremental graded exercise test (GXT) protocols. Typically, these protocols consist of continuous fixed power output increments of 10 to 16 W min^{-1}, until volitional exhaustion (Bell et al., 1988; Mcphee et al., 2010; Neary & Wenger, 1986; Ogita et al., 2000; Rud et al., 2012).

Due to the rigid prescriptive nature of the GXT protocols (Noakes, 2008) and evolving from previous research on sub-maximal perceptually regulated exercise (Eston et al., 2008; Eston et al., 2006; Eston et al., 2005), a novel incremental 5x2 min stages self-paced test (SPT) anchored to the rate of perceived exertion (RPE) levels, has emerged as a valid maximal exercise testing protocol (Mauger & Sculthorpe, 2012). In healthy populations this exertion regulated protocol has been shown to induce similar or higher VO_{2max} values compared to GXTs, both for double-leg cycling (Chidnok et al., 2013a; Mauger & Sculthorpe, 2012) and treadmill running exercise testing (Faulkner et al. 2015; Hogg et al., 2015; Mauger et al., 2013). Importantly, the continuous adjustment of the work rate may also reduce peripheral pain and discomfort during testing (Mauger & Sculthorpe, 2012). The short duration, closed-loop design and individually orientated subjective intensities of the SPT, as well as the possibly lower peripheral discomfort elicited, could be advantageous for clinical SLC exercise testing, especially following knee surgery. To the best of our knowledge the SPT concept has never been used in SLC. Therefore, the purpose of this research is to examine the reliability of a 5x2 min SPT protocol for SLC exercise testing.

3. Methods

Participants

Ten male recreationally active participants (age 27 ± 6 years old, stature 1.75 ± 0.07 m, body mass 77 ± 14 kg) without previous experience of SLC, took part in this study. All participants gave their written informed consent and reported not to have any musculoskeletal or cardiovascular contraindications to exercise testing, as well as being free from any illness or infection during the previous two weeks. On test days, participants were instructed to come to the laboratory in a rested state, having completed no high-intensity exercise within the previous 24 hours, and having abstained from food, alcohol, sports drinks or caffeine intake for the preceding 3 hours. Testing was conducted at the same time of day (± 2 hours) and the visits were separated by at

least 48 hours. This study was reviewed and approved by the University of Kent Research Ethics Committee.

Experimental Design

Participants visited the laboratory on 4 occasions within a 2-week period. In the first visit participants were familiarised with the study procedures, Borg 6-20 RPE scale (Borg, 1970) and SLC. The familiarization consisted of 6-10 min cycling at different RPE intensities to allow participants to adequately coordinate the task and manage the self-pacing efficiently. In the following 3 sessions (S1, S2, and S3), participants repeated a SLC maximal SPT. The test leg was randomly assigned during the first visit and maintained in all sessions. Throughout all SLC tests, the foot of the exercising leg was securely fastened to the pedal and foot of the inactive leg rested comfortably on a stable platform of approximately 40 cm height (Mcphee et al., 2010).

Testing Protocol

The single-leg cycling maximal SPT was performed using an air-braked cycle ergometer (Wattbike Ltd, Nottingham, UK). Immediately before each test, following a 2-min warm-up at light intensity (RPE 11) and 2-min baseline at rest on the bike, verbal instructions with memory anchoring (adapted from Evans, Parfitt & Eston, 2013) were given to the participants on how to use the RPE during the test (see Appendices). The SPT design was similar to that employed by Mauger and Sculthorpe (2012), consisting of 5x2 min stages, where for each stage the subjects were asked to vary their power output according to their perception of effort using the RPE scale. Each stage was anchored to a RPE fixed level. Stage 1 (0 to 2 min) was anchored at an RPE of 11, stage 2 (2 to 4 min) anchored at an RPE of 13, stage 3 (4 to 6 min) anchored at an RPE of 15, stage 4 (6 to 8 min) anchored at an RPE of 17 and stage 5 (8 to 10 min) anchored at an

RPE of 20. During the protocol, subjects were continually reminded of the RPE they should be cycling at and the RPE scale was always on view to the participants.

Measurements

Throughout the 3 cycling tests, pulmonary gas exchange was measured using a breath-by-breath gas analysis system (Cortex Metalyser, 3B, Leipzig, Germany). The system was calibrated before each test with gases of known concentration (16% for O_2, and 5% for CO_2) and the turbine volume transducer was calibrated using a 3-L syringe (Hans Rudolph, MO). Oxygen uptake (VO_2), carbon dioxide (VCO_2), respiratory exchange ratio (RER) and minute ventilation (VE) were calculated and displayed breath-by-breath. The peak VO_2 (VO_{2peak}), peak RER (RER_{peak}) and peak VE (VE_{peak}) were defined as the highest 30 s rolling-mean values recorded before termination of each test. Heart rate (HR) was measured continuously during all tests using short-range radiotelemetry (Polar S610, Polar Electro Oy, Kempele, Finland). Peak HR (HR_{peak}) was defined as the mean HR measured over the final 15 s of each test. The power output per revolution was recorded using the manufacturer computer software (Wattbike Ltd, Nottingham, UK) and averaged in 1 s intervals. The air-braked ergometer used calculates the power output by measuring the chain tension over a load cell (sampled at 100 Hz). The peak power output (PPO) was defined as the highest 30 s rolling-mean power output values recorded. A finger prick blood sample was taken 1 min post-testing and the lactate concentration analysed ($BL_{1\text{-}min}$) (YSI 1500, Yellow Springs Instruments, Yellow Springs, OH).

Statistics

All data are presented as means ± standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate for both experiments. Greenhouse-Geisser correction to degrees of freedom was applied when violations of sphericity were present. For reliability statistics, assumptions of homoscedasticity and heteroscedaticity were checked as appropriate. The reliability analysis was conducted following the guidelines provided by Atkinson and Nevill (1998). One-way repeated measures ANOVA were applied to compare the PPO, VO_{2peak}, HR_{peak}, RER_{peak}, VE_{peak} and $BL_{1\text{-}min}$ between the 3 sessions. Session pairwise comparisons (S1 vs. S2, S1 vs. S3 and S2 vs. S3) were then conducted applying the Bonferonni-Holm correction. Despite not providing a direct index of reliability, the repeated measures ANOVA with the appropriate post-hoc test are commonly used to assess systematic bias between tests (Atkinson & Nevill, 1998). Relative reliability was calculated with the intraclass correlation (ICC) model (2,3). Since all the analysed variables were homoscedastic the standard error of measurement (SEm) was calculated as follows: $SEm = SD \times \sqrt{(1\text{-}ICC)}$. The minimal detectable change (MDC) was calculated as follows: MDC = *z*-score (95% CI) × SEm × √2 (Haley and Fragala-Pinkham, 2006). Bland and Altman's 95% limits of agreement were also calculated (S1 vs. S2, S1 vs. S3 and S2 vs. S3). As data were homoscedastic, only the raw data Bland and Altman's plots are presented. Limit of agreement ratio (LOA) was calculated as follows: LOA = (1.96×SDdiff/grand mean) × 100; where "SDdiff" represents the SD of the differences between tests (S1 vs. S2, S1 vs. S3, and S2 vs. S3) and "grand mean" represents ((mean S1+ mean S2+ mean S3)/3). The effect of the sessions (S1, S2, and S3) over time (20 x 30 s mean time points) on power output and VO_2 was assessed through repeated measures two-way ANOVAs. Studentized residuals were used to assess normality and the presence of outliers (± 3 SD). Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 22 for Mac OS X (SPSS Inc., Chicago, IL, USA). The partial eta squared (η^2) and Cohen's d effect sizes were calculated with G*Power software (version 3.1.9.2 for Mac OS X, Universität Düsseldorf, Germany).

4. Results

In the three SPT sessions the PPO ranged from 105 to 252 W (S1: 163 ± 44 W, S2: 169 ± 47 W, S3: 166 ± 43 W) and the VO_{2peak} from 36 to 55 mL kg^{-1} min^{-1} (S1: 44 ± 4 mL kg^{-1} min^{-1}, S2: 46 ± 6 mL kg^{-1} min^{-1}, S3: 45 ± 7 mL kg^{-1} min^{-1}). Individual and group PPO and VO_{2peak} coefficient of variation (CV) are presented in Table 10. Table 11 summarizes the results of the repeated measures ANOVAs and the inter-session reliability analysis. No significant difference between the 3 sessions were found for PPO ($F_{(2,18)}$=2.829, P=0.085), HR_{peak} ($F_{(2,18)}$=0.256, P=0.777) and VO_{peak} ($F_{(2,18)}$=1.578, P=0.234). The same was observed for RER_{peak}, VE_{peak} and $BL_{1\text{-}min}$. The pairwise comparison with Bonferroni-Holm correction of all analysed variables is presented in Figure 7. This analysis revealed only a significant PPO increase from S1 to S2 of 6 (95% CI, 2 to 10) W (P=0.03, d=0.34). The reliability within the 3 sessions on the analysed variables ranged from acceptable to good (Table 10). The ICC (95% confidence interval) for PPO, VO_{2peak} and HR_{peak} was 0.904 (0.754-0.953), 0.852 (0.645-0.957) and 0.840 (0.613-0.953), with a SEm of 1.45 W, 0.85 mL kg^{-1} min^{-1} and 2 beats min^{-1}, respectively. The MDC for PPO was 4.02 W and for VO_{2peak} was 2.35 mL kg^{-1} min^{-1}. $BL_{1\text{-}min}$ showed the lowest ICC, 0.682 (0.352-0.898) with a SEm of over 0.5 and a MDC of 1.52 mmol L^{-1}. Bland and Altman's plots with 95% limits of agreement between the 3 sessions (S1 vs. S2, S1 vs. S3 and S2 vs. S3) are shown in Figure 8. For PPO, VO_{2peak} and HR_{peak} the limits of agreement were ± 15 W, ± 7 mL kg^{-1} min^{-1} and ± 14 beats min^{-1}, correspondingly. The mean power output, cadence and VO_2 profiles throughout the 3 sessions are represented in Figures 9 and 10. No statistically significant two-way interaction between session and time were found for power output, cadence and VO_2 (P≥0.322). Contrary to time (P<0.001, partial η^2≥0.921), session was not a main effect of neither power output (P=0.074), cadence (P=0.124) and VO_2 (P=0.091).

Table 10 - Individual peak power output and peak oxygen uptake data

	S1		S2		S3		Mean		CV (%)	
Subject	**PPO**	**VO_{2peak}**	**PPO**	**VO_{2peak}**	**PPO**	**VO_{2peak}**	**PPO**	**VO_{2peak}**	**PPO**	**VO_{2peak}**
1	158	47	159	47	157	53	158	49	0.63	7.07
2	154	43	154	48	161	44	156	45	2.59	5.88
3	133	41	136	44	138	47	136	44	1.85	6.82
4	105	37	110	39	108	37	108	38	2.34	3.07
5	112	46	116	47	115	44	114	46	1.82	3.34
6	211	47	217	49	198	48	209	48	4.65	2.08
7	160	51	165	56	166	47	164	51	1.96	8.78
8	249	53	263	52	252	55	255	53	2.89	2.86
9	184	38	201	36	205	36	197	37	5.67	3.15
10	163	34	164	38	158	37	162	36	1.99	5.73
Mean (SD)	163 (44)	44 (4)	169 (47)	46 (6)	166 (43)	45 (7)	166 (44)	45 (6)	2.64 (1.48)	4.88 (2.26)

S1, session 1; S2, session 2; S3, session 3; PPO, peak power output, VO_{2peak}, peak oxygen uptake; CV, coefficient of variation. PPO expressed in W and $VO2_{peak}$ expressed in mL kg^{-1} min^{-1}.

Table 11 - Differences between sessions and inter-session reliability

	Session				Inter-session reliability			
	1	**2**	**3**	***P***	**HTC (R^2)**	**ICC (95% CI)**	**SEm**	**MDC**
PPO (W)	163 (44)	169 (47)	166 (43)	0.085	No (0.097)	0.904 (0.754-0.953)	1.45	4.02
VO_{2peak} (mL kg^{-1} min^{-1})	44 (6)	46 (6)	45 (7)	0.234	No (0.001)	0.852 (0.645-0.957)	0.85	2.35
HR_{peak} (beats min^{-1})	169 (14)	171 (12)	172 (12)	0.777	No (0.007)	0.840 (0.613-0.953)	1.78	4.93
RER_{peak}	1.22 (0.09)	1.19 (0.08)	1.20 (0.08)	0.440	No (0.001)	0.732 (0.425-0.916)	0.01	0.03
VE_{peak} (L min_{-1})	128.9 (27)	136.1 (29.8)	139 (27.6)	0.167	No (0.005)	0.733 (0.429-0.916)	4.51	12.5
BL_{1-min} (mmol L^{-1})	10.08 (1.97)	10.5 (1.67)	10.75 (1.85)	0.357	No (0.009)	0.684 (0.342-0.899)	0.55	1.52

Data are presented as mean (SD). VO_{2peak}, peak oxygen uptake; HR_{peak}, peak heart rate; RER_{peak}, peak respiratory exchange ratio; VE_{peak}, peak minute ventilation; PPO, peak power output; BL_{1-min}, 1 min post-test blood lactate; HTC, heteroscedascity; ICC, intraclass correlation; SEm, standard error of measurement, MDC, minimal detectable change.

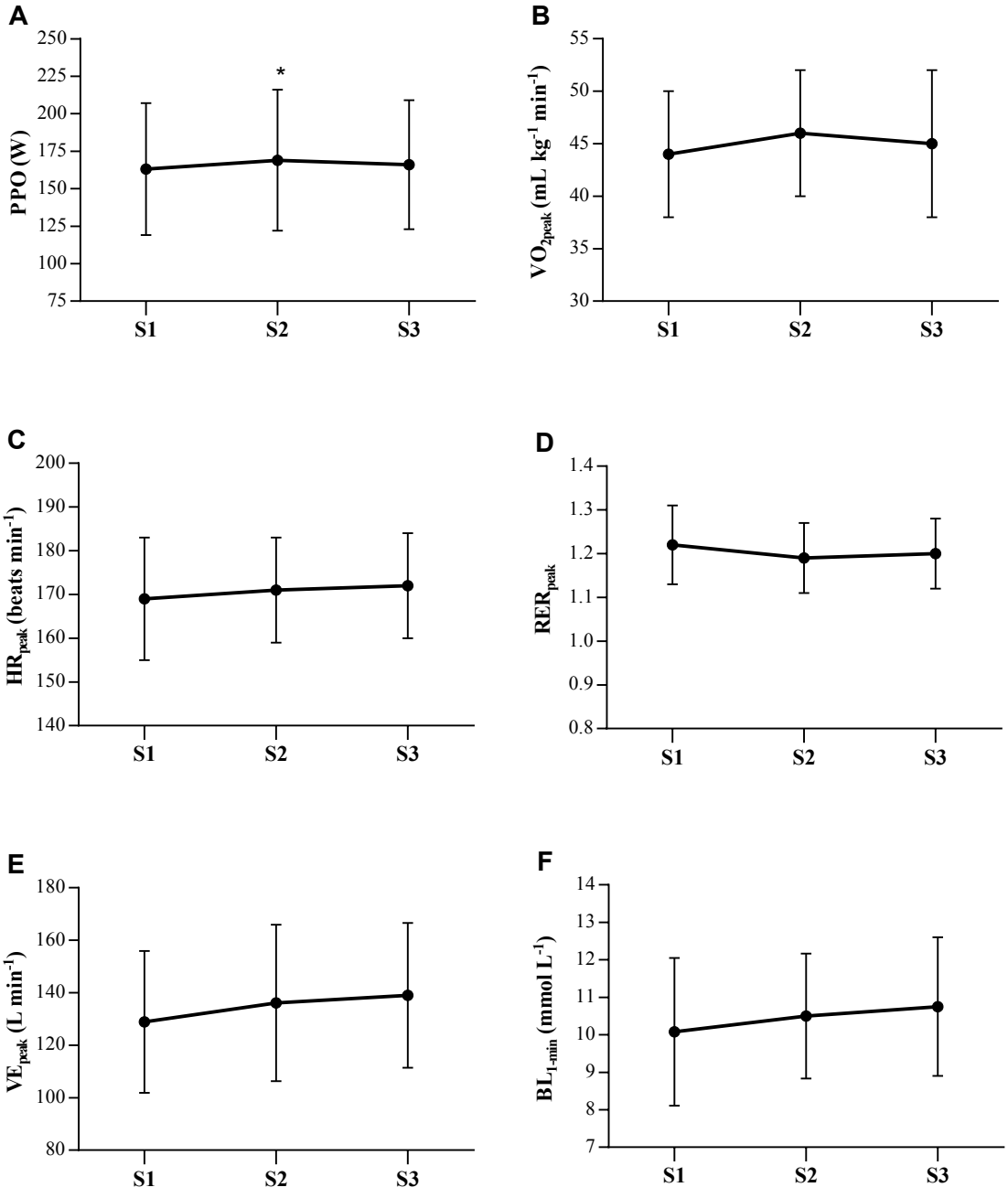

Figure 7 - Pairwise differences between single-leg cycling self-paced tests

Panels: peak power output (A), peak oxygen uptake (B), peak heart rate (C), peak respiratory exchange ratio (D), peak minute ventilation (E), and 1-min post test blood lactate (F). S1, session 1; S2, session 2; S3, session 3. *P<0.05 vs. S1. Data are presented as mean ± SD.

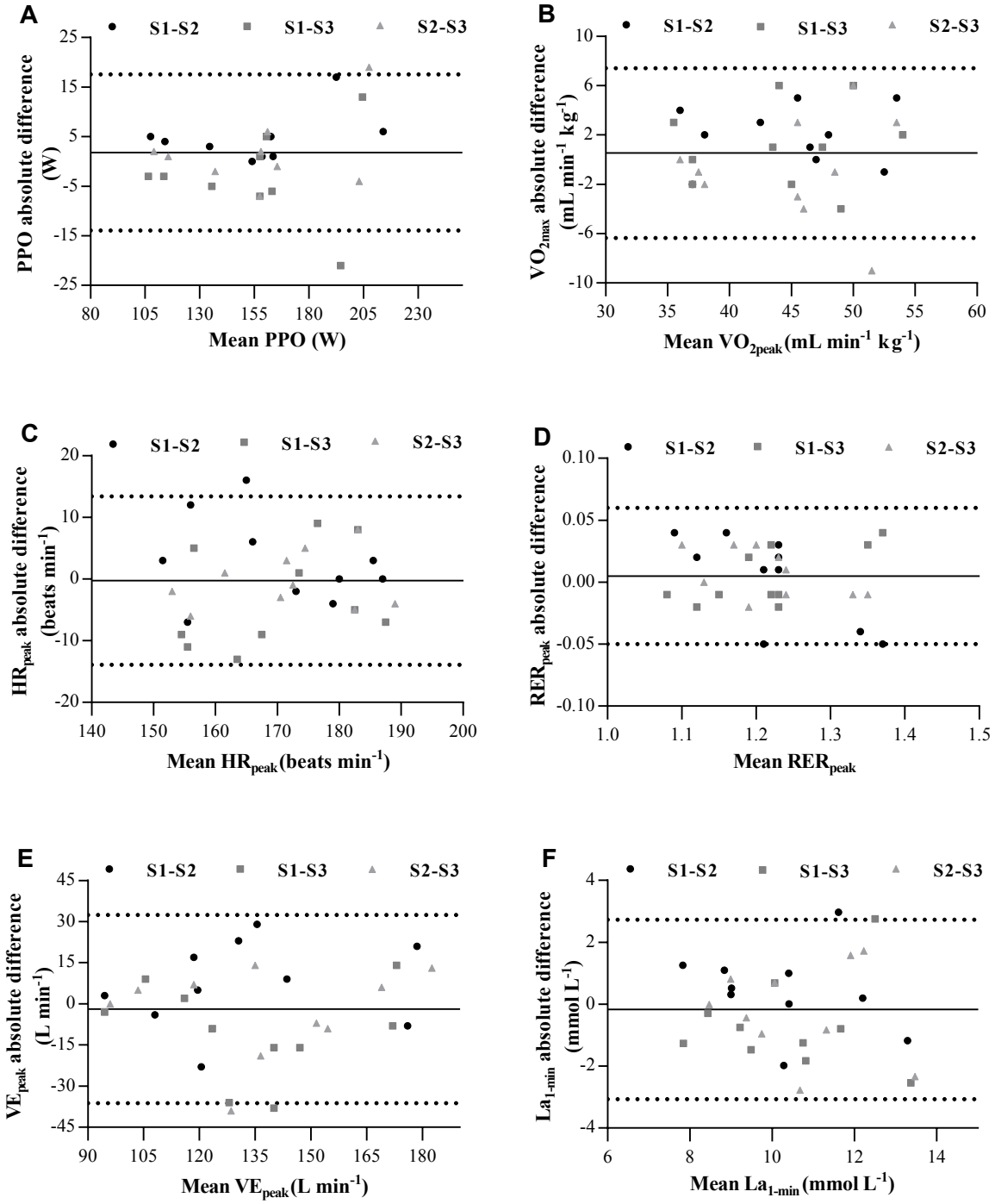

Figure 8 - Raw data Bland and Altman's plots between sessions

Panels: maximal power output (A), maximal oxygen uptake (B), maximal heart rate (C), maximal respiratory exchange ratio (D), maximal minute ventilation (E), and 1-min post-test blood lactate (F). S1, session 1; S2, session 2; S3, session 3. The differences between sessions (S1-S2, S1-S3, S2-S3) are plotted against each individual´s mean of the respective two tests. The grand mean and the limits of agreement are represented by the horizontal continuous line and dashed lines, respectively.

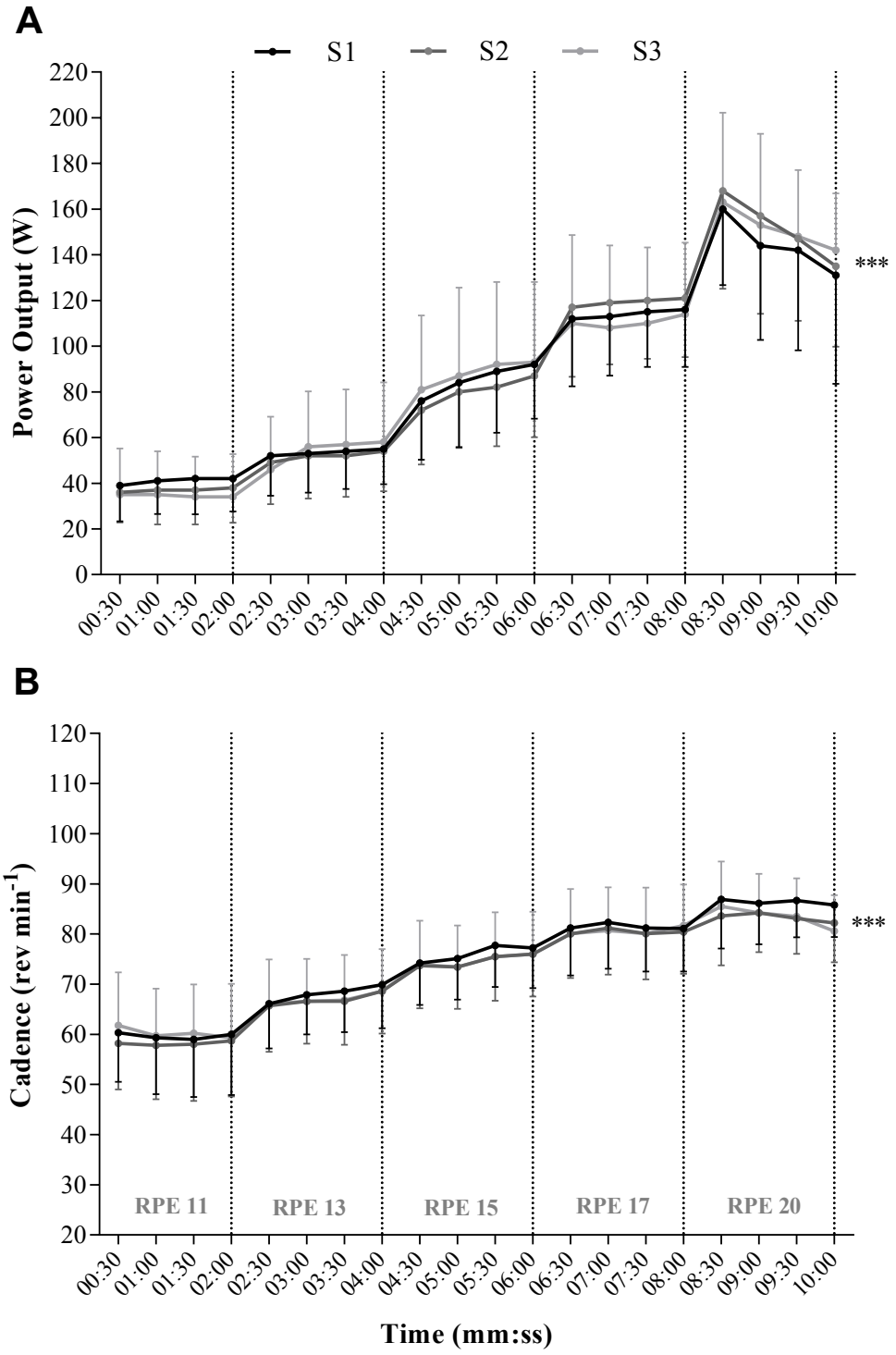

Figure 9 - Power output and cadence profiles throughout the single-leg cycling self-paced tests

Panels A and B represent the power output cadence, respectively. The vertical dashed lines delimit the protocol´s 5 x 2 min stages clamped on the rate of perceived exertion scale. S1, session 1; S2, session 2; S3, session 3. ***Significant main effect of time ($P<0.001$). Data are presented as mean ± SD.

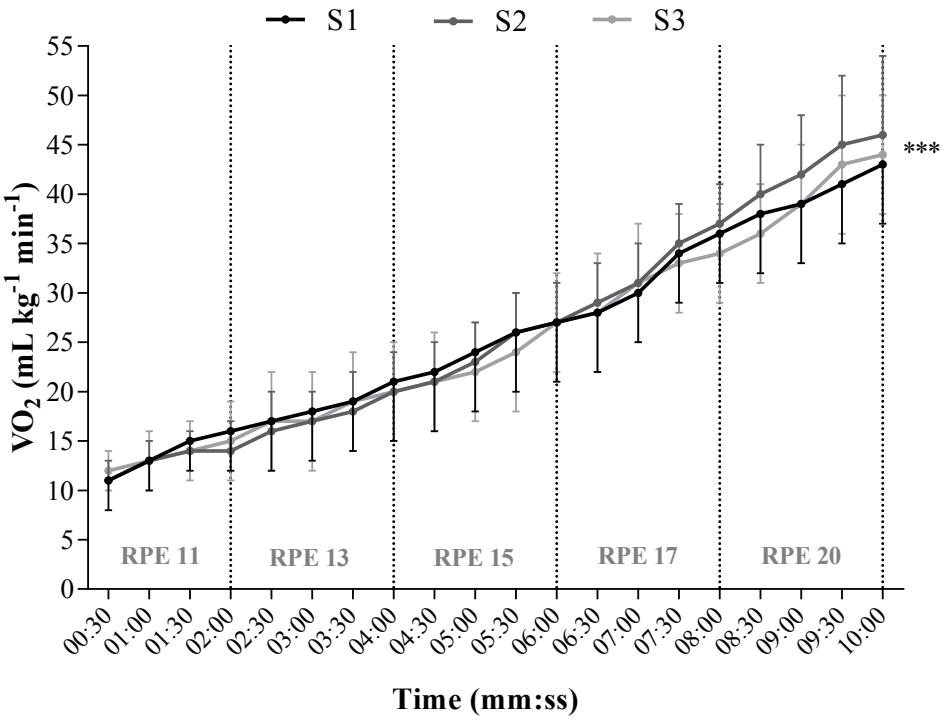

Figure 10 – Oxygen uptake throughout the single-leg cycling self-paced tests

The vertical dashed lines delimit the protocol´s 5 x 2 min stages clamped on the rate of perceived exertion scale. S1, session 1; S2, session 2; S3, session 3. ***Significant main effect of time (P<0.001). Data are presented as mean ± SD.

5. Discussion

In this research, the SPT concept that has been previously used in double-leg cycling and treadmill running, was for the first time introduced to SLC exercise testing. Our results demonstrate that in healthy individuals a closed-loop 5x2 min stages SPT protocol, where participants are allowed to vary their work rate to match 5 incrementally ordered RPE levels (11, 13, 15, 17 and 20), may elicit reliable physiological responses to SLC maximal exercise testing.

All SLC tests fulfilled ≥ 2 secondary criteria for a valid assessment of maximal aerobic capacity: RER ≥ 1.10, end-exercise blood lactate concentration ≥ 8 mmol L^{-1} and a RPE ≥ 17 (ACSM, 2006). Moreover, the mean percentage of the predicted HR_{peak} (220 - age) achieved within the 3 sessions (87 to 89 %) was close to the 90 % threshold; though, this might be considered a problematic criterion (Howley, Bassett, & Welch 1995). The 3 SLC SPTs elicited similar maximal cardiorespiratory and metabolic responses (i.e., VO_{2peak}: 44 ± 6 vs. 46 ± 6 vs. 45 ± 7 mL kg^{-1} min^{-1}), without the apparent presence of a learning effect, (Figure 7).

The reliability of the physiological responses was assessed both through indexes of relative and absolute reliability as recommended for sports medicine research (Atkinson & Nevill, 1998). Since there is not a universally agreed method to measure reliability, a combination of approaches is more likely to give a true picture of reliability (Keszei et al., 2010). Relative reliability is the degree to which individuals maintain their position in a sample over repeated measurements, and is typically expressed by the ICC. This correlation coefficient is used to evaluate both systematic and random errors that may affect relative test–retest reliability (Atkinson & Nevill, 1998). The SPT protocol has revealed good relative reliability, observed by a high ICC in all analysed variables (ICC > 0.75) (Portney & Watkins, 2009) with the exception of the $BL_{1\text{-}min}$ (ICC = 0.684). However, it is important to acknowledge that the threshold to interpret the ICC scores is debateable (Morrow & Jackson, 1993); thus, the practical significance of its value has to be determined with caution. The absolute reliability describes the within-subject variability attributable to repeated measures. This was assessed by the SEm, MDC and the Bland and Altman´s graphical representation of the agreement between sessions. The SEm measures response stability by estimating the standard error

in a set of repeated scores and the MDC represents the magnitude of real change between measurements necessary to exceed error and measurement variability (Haley & Fragala-Pinkham, 2006). The small SEm (i.e., VO_{2peak}=0.85 mL kg^{-1} min^{-1}), residuals homoscedascity, and relatively narrow 95 % LOA seen in the Bland-Altman plots (Figure 3) are good indicators absolute reliability. The MDC values provided can be used as benchmarks for future SLC studies using the SPT. As example, our results showed that a $VO2_{peak}$ difference between tests < 2.35 mL kg^{-1} min^{-1} might be attributable to chance or measurement error.

The reliability results observed are difficult to compare with previous SLC or SPT research. Surprisingly, to the best of our knowledge, only one published study reported reliability information for SLC exercise testing (McPhee et al., 2010). In a study aiming to evaluate the inter-individual variability in adaptation of the leg muscles following training, McPhee et al. (2010) reported a VO_{2peak} CV of 6 % between 2 SLC conventional incremental tests. This value compares favourably with the VO_{2peak} CV observed in our study (4.9 %). Furthermore, our results cannot be compared with previous double-leg cycling studies that used a SPT protocol, since no test-retest or other reliability analysis has been provided (Chidnok et al., 2013a; Mauger & Sculthorpe, 2012). The only reliability data available for the SPT is from a study conducted in a non-motorised treadmill (Mauger et al., 2013) where a test-retest analysis has shown a relatively low VO_{2max} CV (3.7%). Looking at the mean power output, cadence and VO_2 profiles of the 3 SPT sessions (Figures 9 and 10), a close matching between the tests is visually noticeable. This match is corroborated by the repeated measures analysis, since session was not a main effect for any of these variables.

The mean peak power output observed at the beginning of the last stage (159 ± 38 to 167 ± 41 W) and subsequent power output drop (15 to 17 %), mimics what has previously been observed for double-leg cycling by Mauger and Sculthorpe (2012). These authors explain this pattern as the subjects' inability to maintain the initial peak in power output at 20 RPE for the entire duration of the stage, therefore an anticipatory power output drop allows the subject to complete the test. However, a different study using a SPT protocol with 7 RPE stages (8, 10, 12, 14, 16, 18 and 20) showed a less evident drop in mean power output following the initial peak (Chidnok et al., 2013a). This was because participants attained their peak at different times during the last stage (Chidnok et al., 2013b). Due to the increased peripheral fatigue associated with SLC,

the PPO during a SPT is not likely to be attained after the first minute at 20 RPE, as seen in all subjects' tests.

This study presents several limitations. A main limitation was the nature of the sample tested. All participants, despite having no previous experience performing SLC, were healthy and relatively young recreationally active individuals. Thus, the results observed may be different for females, sedentary individuals, and aged or clinical populations. Another possible limitation was the non-usage of an assisting system to help the pull phase of the pedaling cycle during SLC, such as a counterweight (Burns et al., 2014a) or a fixed-flywheel system (Dolmage & Goldstein, 2006). Although in the literature, most of the clinical SLC exercise testing has been performed without any assisting device (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Olivier et al., 2010; Olivier et al., 2008; Wezenberg et al., 2012). Insufficient SLC or exercise protocol familiarization protocol may also have been potential limitations of this study. However, we made all effort to assure all individuals had sufficient SLC training and completely understood the SPT protocol. Moreover, as aforementioned no evident learning effects were observed between sessions.

6. Conclusion

SLC exercise testing both in healthy and clinical populations has been exclusively performed using conventional incremental protocols. This investigation demonstrates that in healthy individuals a closed-loop 5x2 min stages perceptually regulated protocol elicits reliable cardiorespiratory and metabolic responses. The self-paced concept has the potential to be an alternative to conventional protocols for assessing cardiorespiratory deconditioning and reconditioning in clinical populations, particularly in athletes following knee injury and/or surgery. Nevertheless, before the introduction of the SPT in clinical SLC exercise testing, further research should assess its reliability in females, untrained, middle-aged and elderly populations, as well as its validity comparatively to conventional SLC GXT protocols.

CHAPTER 2: VALIDITY OF SELF-PACED SINGLE-LEG CYCLING EXERCISE TESTING

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1. Abstract

The self-paced test (SPT) concept has been shown to elicit reliable peak cardiorespiratory and metabolic responses in single-leg cycling (SLC) exercise testing. However, the validity of these responses has never been studied. Therefore, the aim of this study is assess the validity of a SPT against a conventional SLC graded exercise test (GXT) protocol. Eleven recreationally active male participants (age 29 ± 4 years, stature 1.79 ± 0.06 m, body mass 78 ± 10 kg), with no previous experience in SLC, took part in this study. Participants visited the laboratory on 3 occasions. A double-leg cycling exercise test and SLC cycling familiarization were conducted in visit 1. In visits 2 and 3, in a randomized order, subjects completed a SLC GXT or a SLC SPT. The GXT protocol consisted of 15 W min^{-1} step increments until volitional exhaustion, starting from unloaded. The SPT protocol consisted of 5x2 min stages, where for each stage subjects were asked to vary their power output to match incrementally ordered RPE levels (11, 13, 15, 17 and 20). No differences between protocols were found in peak power output (PPO), peak oxygen uptake (VO_{2peak}), peak heart rate (HR_{peak}), peak respiratory exchange ratio (RER_{peak}), peak minute ventilation (VE_{peak}), 1 min post-test blood lactate ($BL_{1\text{-}min}$) and peak pain ($Pain_{peak}$). Although, the oxygen uptake (VO_2) profile throughout the tests was significantly higher in the SPT ($P<0.005$). The Liking score was also significantly higher in the SPT ($P=0.01$). A 5x2 min stages SPT may provide a valid means for assessing peak aerobic capacity in SLC exercise testing, with increased activity enjoyment, compared to conventional GXT.

2. Introduction

In athletes, severe knee injury and surgery leads inevitably to physical inactivity and long periods of training cessation (Olivier et al. 2007). This may result in partial or complete loss of previously acquired physiological and performance adaptations (Coyle, 1988; Hawley & Burke, 1998), a process described as detraining (Mujika & Padilla, 2000a; Mujika & Padilla, 2000b). In endurance-trained athletes, the cardiorespiratory deconditioning is particularly rapid (Mujika & Padilla, 2003). Previous research has shown that maximal oxygen uptake (VO_{2max}) may decline up to 20 % with more than 3 weeks of training absence (Coyle et al., 1984; Mankowitz et al., 1992; Martin et al., 1986). Nevertheless, most of the evidence gathered on detraining has been based on voluntary training refrains, off season breaks (Mujika & Padilla, 2003), and bed rest studies (Lee et al., 2010). One of the few clinical studies published, conducted following anterior cruciate ligament (ACL) surgical reconstruction, has reported a 10 % drop in peak oxygen uptake (VO_{2peak}) after 6 weeks into the rehabilitation programme (Olivier et al., 2010).

The healing process, range of movement, and limb weight-loading restrictions often are contraindications to conventional exercise testing modalities following knee surgery (Kvist, 2004; van Grinsven et al., 2010). Exercise testing involving the healthy limbs, such as arm cranking or single-leg cycling (SLC), have been used to overcome this limitation (Olivier et al., 2010; Olivier et al., 2008), with the lower perceived exertion and blood lactate concentration reported for SLC, making it better tolerated than arm cranking (Olivier et al., 2008). Moreover, for lower limb rehabilitation purposes arm cranking may not be as effective as SLC. SLC exercise testing is generally performed through classical incremental graded exercise test (GXT) protocols. Typically, these protocols consist of continuous fixed power output increments, ranging from 10-16 W min^{-1} until volitional exhaustion (Bell et al., 1988; Mcphee et al., 2010; Neary & Wenger, 1986; Ogita et al., 2000; Rud et al., 2012). Longer incremental steps (Olivier et al., 2010; Olivier et al., 2008) or smaller power output increments (Bjorgen et al., 2009a; Bjorgen et al., 2009b) have also been used with clinical populations.

For cycling and treadmill running maximal exercise testing, a 5x2 min stages effort perceptually regulated self-paced test (SPT) has emerged as a valid alternative to conventional incremental testing. The SPT allows individuals to pace themselves by continuously adjust work rate to match progressively ordered rate of perceived exertion (RPE) levels. Multiple studies have shown that it elicits similar or even higher VO_{2max} than traditional incremental protocols (Chidnok et al., 2013a; Faulkner et al., 2015; Hogg et al., 2015; Mauger et al., 2013; Mauger & Sculthorpe, 2012). The SPT's short duration, closed-loop design, subjective intensities, as well as the possibly lower peripheral discomfort elicited, may be advantageous for SLC exercise testing. A previous study from our laboratory (Thesis Part II, Chapter 1) has shown that the SPT may elicit reliable peak cardiorespiratory and metabolic responses in healthy young, male individuals. Although, it is not known if these responses compare well with those elicited by conventional SLC exercise testing. Consequently, the purpose of this study is to analyse the validity of a SPT against a SLC GXT protocol. We hypothesised that the SPT would elicit similar physiological responses, with possibly improved activity enjoyment, comparatively to the GXT.

3. Methods

Participants

Eleven recreationally active male participants (age 29 ± 4 years, stature 1.79 ± 0.06 m, body mass 78 ± 10 kg) took part in this study. Before initiating the study, all participants gave their written informed consent. They also reported not to have any musculoskeletal or cardiovascular contraindications to exercise testing and were free from any illness or infection during the previous two weeks. On test days, participants were instructed to come to the laboratory in a rested state, having completed no high-intensity exercise within the previous 24 hours, and having abstained from food, alcohol, sports drinks or caffeine intake for the preceding 3 hours. Testing was conducted at the same time of day (± 2 hours) and the visits were separated by at least

48 hours. This study was reviewed and approved by the University of Kent Research Ethics Committee.

Experimental Design

This experiment consisted of 3 sessions completed over a 10 day period. In the first session, following the study procedures and RPE scale familiarisation, participants performed a double-leg cycling GXT. Thirty minutes after the completion of the test, subjects started a 6-10 min SLC familiarisation at different intensities on both air- and electronically-braked ergometers. In the second and third visits, in a randomised order, subjects performed a SLC maximal GXT or a SPT. The tested leg was randomly assigned and maintained during both protocols. Throughout all single-leg cycling tests, the foot of the exercising leg was securely fastened to the pedal and the foot of the inactive leg rested comfortably on a stable platform approximately 40 cm high (Mcphee et al., 2010).

Exercise Testing Protocols

Double-leg cycling GXT**:** this test was performed on an electronically-braked cycle ergometer (Lode, Excalibur Sport, Groningen, Netherlands) following a 10 min warm up at 50 W. The test started unloaded and increased by 25 W step increments every minute. Participants were instructed to maintain their preferred cadence throughout the test. The test was terminated upon volitional exhaustion or when cadence could no longer be maintained (i.e., dropped by > 10 rpm).

Single-leg cycling SPT**:** this test was performed using an air-braked cycle ergometer (Wattbike Ltd, Nottingham, UK). Immediately before each test, following a 2 min warm-up at light intensity (RPE 11) and 2 min baseline at rest on the bike, verbal instructions with memory anchoring (adapted from Evans et al., 2013) were given to the

participants on how to use the RPE during the test (see appendices). The SPT design was similar to Mauger and Sculthorpe (2012), consisting of 5x2 min stages, where for each stage the subjects were asked to vary their power output according to their perception effort, using for that the RPE. Each stage was anchored to a RPE fixed level. Stage 1 (0 to 2 min) was anchored at an RPE of 11, stage 2 (2 to 4 min) anchored at an RPE of 13, stage 3 (4 to 6 min) anchored at an RPE of 15, stage 4 (6 to 8 min) anchored at an RPE of 17 and stage 5 (8 to 10 min) anchored at an RPE of 20. During the protocol, subjects were continually reminded of the RPE they should be cycling at and the RPE scale was always on view to the participants.

Single-leg cycling GXT**:** this test was performed on the same ergometer as for the double-leg cycling test. Following a 2 min warm-up at 20 W and 2 min baseline at rest on the bike, the SLC test started unloaded and increased by 15 W step increments every minute. Subjects were instructed to maintain their preferred cadence throughout the test and the termination criteria were similar to normal cycling.

Measurements

Throughout all cycling tests, pulmonary gas exchange was measured using a breath-by-breath gas analysis system (Cortex Metalyser, 3B, Leipzig, Germany). The system was calibrated before each test with gases of known concentration (16% for O_2, and 5% for CO_2) and the turbine volume transducer was calibrated using a 3 L syringe (Hans Rudolph, MO). Oxygen uptake (VO_2), carbon dioxide (VCO_2), respiratory exchange ratio (RER) and minute ventilation (VE) were calculated and displayed breath-by-breath. The VO_{2peak}, peak RER (RER_{peak}) and peak VE (VE_{peak}) were defined as the highest 30 s rolling-mean values recorded before termination each test. Heart rate (HR) was measured continuously during all tests using short-range radiotelemetry (Polar S610, Polar Electro Oy, Kempele, Finland). Peak HR (HR_{peak}) was defined as the mean HR measured over the final 15 s of each test. During the SPT the power output per revolution was recorded using the manufacturer computer software (Wattbike Ltd, Nottingham, UK). The power output per revolution was later averaged in 1 s intervals.

This air-braked ergometer calculates the power output by measuring the chain tension over a load cell (sampled at 100 Hz). The peak power output (PPO) was defined as the highest 30 s rolling-mean power output values recorded. In both normal cycling and SLC GXTs, PPO was defined as the mean power output during the last 30 s of each test. A finger prick blood sample was taken 1 min post-testing and the lactate concentration analysed ($BL_{1\text{-}min}$) (YSI 1500, Yellow Springs Instruments, Yellow Springs, OH). Throughout all tests, in the last 10 s of each minute, participants were asked to rate the pain they were feeling in the exercising leg (0-10 points scale), the peak pain ($Pain_{peak}$) reported was considered for analysis. During the GXTs minute RPEs were also collected and the peak RPE considered for analysis (RPE_{peak}). In addition, upon completion of each test, participants were asked to indicate their liking of that specific test via a 10-points Liking score, by placing an "X" on a 10 cm line that was marked at the far left with "did not like it al all", the middle with "neutral", and far right with "liked a lot" (Burns et al., 2014a).

Statistics

All data are presented as means ± standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. The dependent variables analysed were PPO, VO_{2peak}, HR_{peak}, RER_{peak}, VE_{peak}, $BL_{1\text{-}min}$, $Pain_{peak}$, RPE_{peak}, and Liking score. The differences on the dependent variables between the SPT and GXT protocols were determined using paired sample t-tests. The effect of the protocol (GXT, SPT) over time (20 x 30 s mean time points) on power output and VO_2 was assessed through repeated measures two-way ANOVAs. Studentized residuals were used to assess normality and the presence of outliers (± 3 SD). Greenhouse-Geisser correction to degrees of freedom was applied when violations of sphericity were present. All analyses were conducted using the Statistical Package for the Social Sciences, version 22 for Mac OS X (SPSS Inc., Chicago, IL, USA) and the significance was set at 0.05 (2-tailed). The partial eta squared (η^2) and Cohen's d effect sizes were calculated with G*Power software (version 3.1.9.2 for Mac OS X, Universität Düsseldorf, Germany).

4. Results

The mean PPO, VO_{2peak} and HR_{peak} during the normal double-leg cycling GXT were 295 ± 27 W, 50 ± 6 mL kg^{-1} min^{-1} and 172 beats min^{-1}, respectively (Table 12). Comparing both SLC protocols, the GXT was not different from the SPT in PPO (169 ± 26 vs. 168 ± 27 W), VO_{2peak} (42 ± 5 vs. 42 ± 5 mL kg^{-1} min^{-1}), HR_{peak} (162 ± 9 vs. 165 ± 11 beats min^{-1}), RER_{peak} (1.21 ± 0.09 vs. 1.23 ± 0.1), VE_{peak} (131 ± 20 vs 142 ± 27 L min^{-1}), $BL_{1\text{-}min}$ (9.1 ± 1.6 vs 9.1 ± 2.4 mmol L^{-1}), and $Pain_{peak}$ (8 ± 1 vs 9 ± 1). The PPO and VO_{2peak} achieved during both SLC tests corresponded to ≈ 57% and 84% of double leg-cycling PPO and $VO_{2peak,}$ correspondingly. Significant differences between the SLC GXT and SLC SPT were only observed in test duration and Liking score. Two participants finished the SLC GXT before reaching 10 min of duration. Although, on average the GXT was 1 min longer than the SPT (11 ± 1 vs 10 ± 0 min; t(10)= 2.838, P=0.02, d=0.88). Participants preferred the SPT more than the GXT (t(10)=-3.825, P=0.01, d=1.42), with the mean Liking score difference between both protocols was 1.2 (95% CI, 0.53 to 2.01). The power output and VO_2 profiles throughout SLC GXT and SLC SPT are represented in Figures 11A and 11B, respectively. With the exception of the last 30 s, the mean power output throughout the SPT was continuously higher than the GXT fixed power increments (15 W min^{-1}). The highest mean power output during the SPT was attained in the first 30 s of the 20 RPE stage (167 ± 20 W). No statistically significant two-way interaction between the protocol and time was found for power output or VO_2 (P=0.666). Although, both time (P<0.001, partial η^2=0.962) and protocol (P=0.003, partial η^2=0.659) were significant main effects of VO_2. Throughout the SLC SPT duration, the VO_2 was on average 5 mL kg^{-1} min^{-1} (95% CI, 2 to 8) higher than for the SLC GXT.

Table 12. Single-leg cycling self-paced *vs.* graded exercise testing

	Normal Cycling GXT	Single-leg Cycling GXT	Single-leg Cycling SPT
PPO (W)	295 ± 27	169 ± 26	168 ± 27
Test duration (min)	12 ± 1	11 ± 1	10 ± 0*
VO_{2peak} (mL kg^{-1} min^{-1})	50 ± 6	42 ± 5	42 ± 6
HR_{peak}(beats min^{-1})	172 ± 10	162 ± 9	165 ± 11
RER_{peak}	1.28 ± 0.08	1.21 ± 0.09	1.23 ± 0.1
VE_{peak} (L min^{-1})	160 ± 20	131 ± 20	142 ± 27
$BL_{1\text{-}min}$ (mmol L^{-1})	11.3 ± 2.1	9.1 ± 1.6	9.1 ± 2.4
RPE_{peak} §	19 (1)	18 (1)	---
$Pain_{peak}$	9 ± 1	8 ± 1	9 ± 1
Liking score	6 ± 1	4 ± 1	5 ± 1*

Data are presented as mean ± SD. $BL_{1\text{-}min}$, 1 min post-test blood lactate; GXT, graded exercise test; HR_{peak}, peak heart rate; $Pain_{peak}$, peak rate of pain; PPO, peak power output; RER_{peak}, peak respiratory exchange ratio; RPE_{peak}, peak rate of perceived exertion; SPT, self-paced test; VE_{peak}, peak minute ventilation; VO_{2peak}, peak oxygen uptake. §Non-normally distributed variable, data presented as median (interquartile range). *Significant difference between single-leg cycling GXT and SPT ($P<0.05$).

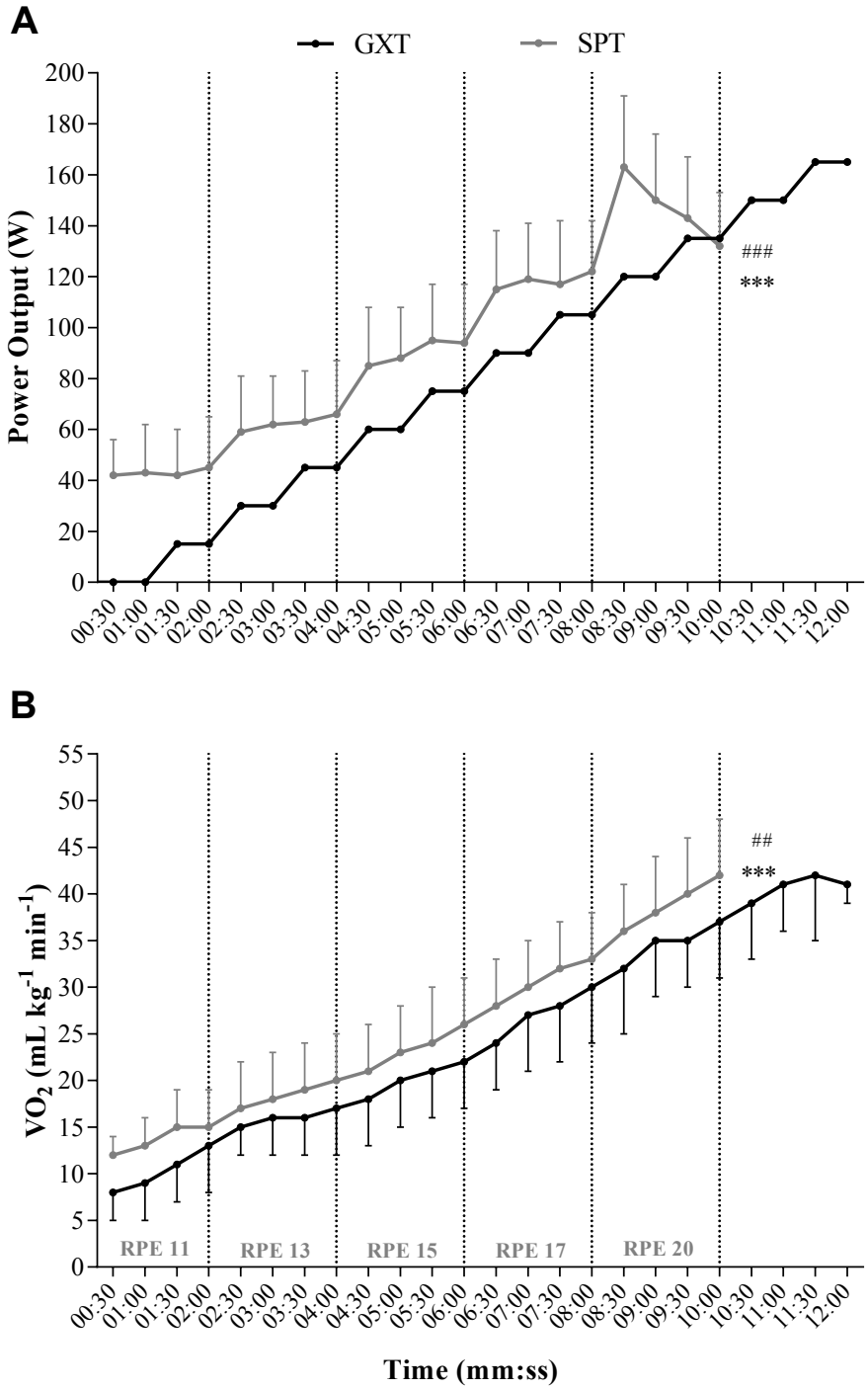

Figure 11 - Power output and oxygen uptake profiles throughout both single-leg cycling exercise testing protocols

Panels A and B represent the power output and the oxygen uptake, respectively. The vertical dashed lines delimit the protocol´s 5 x 2 min stages clamped on the rate of perceived exertion scale. GXT, graded exercise test; SPT, self-paced test. *Significant main effect of time. #Significant main effect of protocol. Two items correspond to $P<0.01$ and three items correspond to $P<0.001$. Data presented as mean ± SD.

5. Discussion

This investigation assessed the SLC SPT protocol validity through a concurrent comparison against a conventional SLC GXT protocol in healthy individuals. Despite a reduced muscle mass activity inherent to SLC, all participants in both protocols met the ≥ 2 secondary criteria for a valid assessment of maximal aerobic capacity, by reaching RER ≥ 1.10, end-exercise blood lactate concentration ≥ 8 mmol L^{-1} and RPE ≥ 17 (ACSM, 2006). The SPT protocol has shown a similar PPO to the GXT (169 ± 26 vs. 168 ± 27 W). However, this correspondence in PPO between both SLC protocols should be interpreted with caution since they were performed on different ergometers (electronically- vs. air-braked). Nevertheless, both protocols elicited similar cardiorespiratory and metabolic responses, seen in VO_{2peak}, HR_{peak} VE_{peak}, RER_{peak} and $BL_{1\text{-}min}$. Throughout the SPT, the highest mean power output occurred at the beginning of the 20 RPE stage, which was followed by a ≈ 20 % drop in power output drop until test termination. This power output variation is analogous to what observed in our previous study (Thesis Part II, Chapter 1) and has been reported as a characteristic pattern of the SPT (Mauger & Sculthorpe, 2012). The SLC PPO attained in both protocols represented ≈ 67 % of the PPO attained during normal-cycling. This value is slightly above the 55 to 65 % MPO ratio reported in previous studies conducted with healthy subjects (Magnusson, Kaijser, Isberg, & Saltin, 1994; Ogita et al., 2000; Rud et al., 2012). Nevertheless, this ratio might be different in clinical population and several SLC studies have not reported it (Bell et al., 1988; Klausen et al., 1982; Neary & Wenger, 1986; McPhee et al., 2010). The ability of SLC to generate higher leg specific power output comparatively to double-leg cycling is directly related to the reduced muscle mass usage and consequently enlarged blood supply to the working muscle mass (Klausen et al., 1982; Magnusson et al., 1994). An early study from Klausen et al. (1982) showed that in untrained individuals, for the same sub-maximal VO_2, SLC might elicit 1.5 L min^{-1} more leg blood flow than double-leg cycling. That study also demonstrated that the maximal leg blood flow is reached during one-leg exercise.

The mean VO_2 observed throughout the SLC SPT was substantially higher than for the SLC GXT, reflecting the difference in power output profile between protocols (Figures 11A). Although, as mentioned, the SPT $VO2_{peak}$ and the other peak variables

were not different than the SLC GXT. This can be explained by the longer duration of the GXT (11 ± 1 vs. 10 ± 0 min) and the similar PPO observed between both protocols. In fact, this difference in duration is a potential confounding factor of this study, since it is known that the VO_2 during incremental exercise may be influenced by the total duration of the tests (Astorino et al., 2004; Midgley, Bentley, Luttikholt, McNaughton, & Millet, 2008). Nevertheless, the SLC VO_{2peak} corresponded to ≈ 85 % of the double-leg cycling $VO2_{peak}$, which is in line with the values previously reported (Klausen et al., 1982; McPhee et al., 2010; Neary & Wenger, 1986; Rud el al., 2012). In terms of the perceptual responses, our results have not shown differences in pain between both SLC protocols but importantly, the majority of participants (70 %) have shown to prefer the SPT over the GXT, seen by the higher Liking score (5 ± 1 vs. 4 ± 1). This is relevant since lack of enjoyment or excessive discomfort is known to negatively affect exercise performance and adherence (Astorino et al., 2011), which is also valid in the context of sports rehabilitation (Chan, Lonsdale, Ho, Yung, & Chan, 2009). Moreover, it highlights the applicability of self-paced protocols in SLC exercise testing, particularly for a clinical population such as following knee injury and/or surgery. Anecdotally, participants reported that the fixed duration and ability to adjust work rate but also cadence throughout the test, makes the SPT easier to perform than the GXT.

Alongside the differences regarding the ergometer used and protocol duration, another potential limitation of this investigation was the non-usage of an assisting system to help the pull phase of the pedaling cycle. These systems usually consist of a counterweight attached to the non-exercising side arm crack (Abbiss et al., 2010; Burns et al., 2014a; Thomas, 2009) or a fixed-flywheel (Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006; Rud et al., 2012), allowing less effort from the hip flexor muscles, possibly improving the SLC rhythm, smoothness and tolerability. A recent study has shown that during sub-maximal SLC a 97 N (approximately 10 kg) counterweight may induce similar cardiovascular responses to double-leg cycling, as well as improving subjects' activity enjoyment compared to non-assisted SLC (Burns et al. 2014a). The fixed-flywheel system has been mostly used in COPD research (Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006). This system requires a manufacturer alteration to the ergometer and is totally dependent on the ergometer flywheel mass (non-adjustable) and resulting kinetic energy storage, because if the mass of the flywheel is small or the power output large the kinetic energy will be insufficient to assist the upward pedal cycle (Burns, Martin, Elmer & McDaniel, 2014b). However,

in most of the clinical studies conducted, SLC exercise testing has been performed without any assisting device (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Olivier et al., 2010; Olivier et al., 2008; Wezenberg et al., 2012).

6. Conclusion

The results of the present study demonstrated that in healthy individuals a 5x2 min stages RPE anchored SLC SPT protocol provide valid means for assessing peak aerobic capacity. The SPT elicited similar peak cardiorespiratory and metabolic responses comparatively to a conventional SLC incremental protocol. However, the test duration difference between protocols is a confounding factor that should be acknowledge. The perceptually regulated protocol has also shown to increase the activity enjoyment and possibly the tolerability to SLC exercise testing, which could be useful for clinical purposes. Further research should consider the test duration influence, as well assess its reliability and validity in the clinical setting, including in athletes following knee injury and/or surgery. Moreover, the effect of assisted SLC exercise testing on physiological and perceptual responses should also be investigated.

CHAPTER 3: THE EFFECT OF A COUNTERWEIGHT ON MAXIMAL SINGLE-LEG CYCLING EXERCISE TESTING

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1. Abstract

Counterweight assisted maximal single-leg cycling (SLC) exercise testing has not been addressed in previous research. Thus, the aim of this study was to investigate the effect of a 10 kg counterweight on cardiorespiratory, metabolic and perceptual responses during SLC exercise testing. Eleven male recreationally active individuals (age 30 ± 4 years, stature 1.79 ± 0.05 m, body mass 77 ± 12 kg) took part in this study. Participants visited the laboratory on 5 occasions. A double-leg cycling exercise test and SLC cycling familiarisation were conducted in visit 1. In visits 2 and 3, in a randomised order, subjects completed a maximal SLC graded exercise test (GXT) without (CW0) or with a 10 kg counterweight (CW10). In visits 4 and 5, the same counterweight settings were used but with a self-paced test (SPT) protocol. The SLC GXT protocol consisted of 15 W min^{-1} step increments until volitional exhaustion, starting from unloaded. The SPT protocol consisted of 5 x-second stages, where x was equal to the duration of the previously completed GXT, for the matching counterweight condition. During each stage of the SPT, participants were asked to vary their power output to match incrementally ordered rate of perceived exertion (RPE) levels (11, 13, 15, 17 and 20). No interaction between main effects of protocol and counterweight type were observed. The SPT protocol and the CW10 resulted in higher peak power output (PPO) and Liking scores. Peak minute ventilation (VE_{peak}) as well peak oxygen uptake (VO_{2peak}) showed a significant main effect of protocol type ($P=0.012$, partial $\eta^2=0.483$). The highest VO_{2peak} was observed in the SPT_{CW10}. No main effects were found for peak heart rate (HR_{peak}), peak respiratory exchange rate (RER_{peak}), peak pain ($Pain_{peak}$) and 1 min post-test blood lactate concentration ($BL_{1\text{-}min}$) ($P\geq0.097$). The CW10, despite of improving the activity enjoyment, does not seem to affect peak cardiorespiratory and metabolic responses to SLC exercise testing. The SPT may elicit higher PPO and $VO2_{peak}$ than conventional SLC incremental protocols regardless of the counterweight usage or not.

2. Introduction

Single-leg cycling (SLC) exercise testing and training has been used with clinical populations when bilateral lower-limb exercise is contraindicated or not possible to perform, such as following knee surgery (Olivier et al., 2010; Olivier et al., 2008) or with lower-limb amputees (Wezenberg et al., 2012). Compared to double-leg cycling, this unilateral exercise modality has been shown to induce increased blood flow to the active muscles (Klausen et al., 1982; Rud et al., 2012) with less cardiovascular and ventilatory stress (Bjorgen et al., 2009b). Thus, it has been also used in patients with chronic pulmonary obstructive disease (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006). Nevertheless, SLC requires an active pull phase of the pedal cycle, imposing an increased activation and fatigue of the hip flexor muscles (Bini et al., 2015), which may cause coordination difficulties (Burns et al., 2014a) and distorted cycling rhythm in weaker individuals (Wezenberg et al., 2012). To overcome this biomechanical limitation, multiple approaches have been reported in the literature, including: tandem cycling (Gleser, 1973); springs system (Freyschuss & Strandell, 1968); electric motor (Koga et al., 2001); and a fixed-flywheel (Dolmage & Goldstein, 2008; Dolmage & Goldstein, 2006; Rud et al., 2012). More recently, different studies have used a 10 kg (≈ 97 N) counterweight device attached to the non-exercising arm crank (Abbiss et al., 2010; Burns et al., 2014a; Thomas, 2009). For matched sub-maximal work rates, this counterweight device has been reported to make SLC more tolerable than non-assisted SLC, eliciting substantially less cardiovascular and peripheral stress (Burns et al., 2014a).

SLC exercise testing has been typically performed through classical incremental graded exercise test (GXT) protocols, consisting in continuous fixed power output increments, until volitional exhaustion (Bell et al., 1988; Mcphee et al., 2010; Neary & Wenger, 1986; Ogita et al., 2000; Rud et al., 2012). However, perception of effort regulated self-paced test (SPT) protocols have emerged as valid alternatives for sub-maximal exercise testing (Eston et al., 2008; Eston et al., 2006; Eston et al., 2005) and more recently, for maximal exercise testing (Mauger & Sculthorpe, 2012). These protocols allow individuals to continuously adjust work rate to match incrementally

ordered rate of perceived exertion (RPE) levels, within a pre-defined test duration. Multiple studies have shown that a maximal SPT may induce similar or even higher maximal oxygen uptake (VO_{2max}) compared to conventional incremental tests, both for double-leg cycling (Chidnok et al., 2013; Mauger & Sculthorpe, 2012) and treadmill running (Faulkner et al., 2015; Hogg et al., 2015; Mauger et al., 2013). Furthermore, previous studies from our laboratory (Thesis Part II: Chapters 1 and 2) have shown that the SPT in SLC exercise testing elicits reliable and valid physiological responses in comparison to conventional GXT protocols. Although, the effect of a counterweight device in maximal SLC exercise testing has not been previously investigated. Therefore, the aim of this study was to assess the effect of a 10 kg counterweight on cardiorespiratory, metabolic and perceptual responses during SLC exercise testing, both through GXT and SPT protocols. We hypothesised that the use of a 10 kg counterweight would elicit lower physiological responses comparatively to non-counterweighted SLC exercise testing, regardless of the protocol type.

3. Methods

Participants

Eleven male recreationally active participants (age 30 ± 4 years, stature 1.79 ± 0.05 m, body mass 77 ± 12 kg) took part in this study. All participants gave their written informed consent and reported not to have any musculoskeletal or cardiovascular contraindications to exercise testing, they were also free from any illness or infection during the previous two weeks. On test days, participants were instructed to come to the laboratory in a rested state, having completed no high-intensity exercise within the previous 24 hours, and having abstained from food, alcohol, sports drinks or caffeine intake for the preceding 3 hours. This research was reviewed and approved by the University of Kent Research Ethics Committee.

Experimental Design

Participants visited the laboratory on 5 occasions within a 2 week period. The visits were separated by a period of 48 hours and occurred at the same period of the day. In the first visit, following study procedures and RPE scale familiarisation, subjects performed a double-leg cycling GXT. Thirty minutes after the completion of the normal double-leg cycling test, subjects started a 6-10 min SLC familiarisation at different intensities without a counterweight (CW0) and with a 10 kg counterweight device (CW10). This familiarisation procedure aimed to allow participants to adequately coordinate the task and manage the self-pacing efficiently. In visits 2 and 3, in a randomised order, participants performed a maximal SLC GXT without counterweight (GXT_{CW0}) or with a 10 kg counterweight (GXT_{CW10}). In visits 4 and 5, also in a randomised order, participants performed a maximal SLC SPT without counterweight (SPT_{CW0}) or with a 10 kg counterweight (SPT_{CW10}). The counterweight was attached to a spindle on the arm crank of the inactive leg. Throughout all tests, the foot of the exercising leg was securely fastened to the pedal and the foot of the inactive leg rested comfortably on a stable platform approximately 40 cm high (Mcphee et al., 2010). The mass of the counterweight was based on previous research (Abbiss et al., 2010; Burns et al., 2014a).

Testing Protocol

All cycling tests were performed on an electronically-braked cycle ergometer (Velotron, Racer-Mate, Inc., Seattle, Washington, USA). The double-leg cycling GXT, which followed a 10 min warm up at 50 W, started at 60 W with step increments of 25 W min^{-1}. The GXT_{CW0} and GXT_{CW10} protocols, after a 2 min warm-up at 20 W, started unloaded and increased by 15 W min^{-1}. In all GXTs, participants were instructed to maintain their preferred cadence consistently throughout the tests. Tests were terminated upon volitional exhaustion or when cadence could no longer be maintained (i.e., dropped by > 10 rpm). Immediately before SPT_{CW0} and SPT_{CW10} start, following a 2 min warm-up at light intensity (RPE 11), verbal instructions with memory anchoring

(adapted from Evans et al., 2013) were given to the participants on how to use the RPE scale during the test (see appendices). The SPT protocol structure was similar to that of Mauger and Sculthorpe (2012) but with an adjustable duration (Chidnok et al., 2013a). The protocol consisted of 5 x-second stages clamped to specific 6-20 RPE levels (Borg, 1970), where x was equal to the duration of the previously done GXT, for the matching counterweight condition. For each stage participants were asked to vary their power output according to their perception of exertion, using for that the RPE scale. Stage 1 was anchored at an RPE of 11, stage 2 anchored at an RPE of 13, stage 3 anchored at an RPE of 15, stage 4 anchored at an RPE of 17 and finally, stage 5 anchored at an RPE of 20. Using this design, subjects can vary their work rate according to the RPE required at each stage, but the progressive RPE clamps allow the test to retain an incremental format (Mauger & Sculthorpe, 2012). During the protocol, subjects were continually reminded of the RPE level they should be cycling at and the RPE scale was always on view to the participants.

Measurements

Throughout all cycling tests, pulmonary gas exchange was measured using a breath-by-breath gas analysis system (Cortex Metalyser, 3B, Leipzig, Germany). The system was calibrated before each test with gases of known concentration (16% for O_2, and 5% for CO_2) and the turbine volume transducer was calibrated using a 3-L syringe (Hans Rudolph, MO). Oxygen uptake (VO_2), carbon dioxide (VCO_2), respiratory exchange ratio (RER) and minute ventilation (VE) were calculated and displayed breath-by-breath. The VO_{2peak}, peak RER (RER_{peak}), and peak VE (VE_{peak}) were defined as the highest 30 s rolling-mean values recorded before each test termination. Heart rate (HR) was measured continuously during all tests using short-range radiotelemetry (Polar S610, Polar Electro Oy, Kempele, Finland). Peak HR (HR_{peak}) was defined as the mean HR measured over the final 15 s of each test. During the SPTs, the power output was recorded using the ergometer manufacturer computer software (Velotron, Racer-Mate, Inc., Seattle, Washington, USA). The peak power output (PPO) of the SPTs was defined as the highest 30 s rolling-mean power output values recorded, and in the GXTs

it was defined as the mean power output of the last 30 s. A finger prick blood sample was taken 1-min post-testing and the lactate concentration analysed ($BL_{1\text{-}min}$) (YSI 1500, Yellow Springs Instruments, Yellow Springs, OH). For all tests, during the last 10 s of each minute, participants were asked to rate the pain they were feeling in the exercising leg (0-10 points scale), and the peak pain ($Pain_{peak}$) reported was used for analysis. During the GXTs, minute RPE was also collected and the highest RPE (RPE_{peak}) reported was used for the analysis. In addition, upon completion of each test, participants were asked to indicate their liking of that specific test via a 10-points Liking score, by placing an "X" on a 10 cm line that was marked at the far left with "did not like it al all", the middle with "neutral" and far right with "liked a lot" (Burns et al., 2014a).

Statistics

All data are presented as means ± standard deviation (SD) unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. The dependent variables analysed were: PPO, VO_{2peak}, HR_{peak}, RER_{peak}, VE_{peak}, $BL_{1\text{-}min}$, $Pain_{peak}$, RPE_{peak} and Liking score. A paired-sample t test was conducted to evaluate the difference in test duration and RPE_{peak} between GXT_{CW0} and GXT_{CW10}. Fully repeated measures 2 x 2 ANOVAs were used to test the effect of the protocol (GXT, SPT) and counterweight setting (CW0, CW10) on the dependent variables. Fully repeated measure 2 x 24 ANOVAs were conducted to test the effect of the counterweight setting (CW0, CW10) and time (every 30 s time points) on power output, cadence and VO_2 throughout the GXTs and SPTs. Studentized residuals were used to assess normality and the presence of outliers (± 3 SD). Greenhouse-Geisser correction to degrees of freedom was applied when violations of sphericity were present. Significant interactions and main effects were followed up with pairwise comparisons using Bonferonni adjustment as appropriate. Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 22 for Mac OS X (SPSS Inc., Chicago, IL, USA). Partial squared eta (η^2) and Cohen's d effect sizes were calculated with G*Power software (version 3.1.9.2 for Mac OS X, Universität Düsseldorf, Germany).

4. Results

The GXT_{CW10} was on average 1 min longer than the GXT_{CW0} (12 ± 1 vs. 11 ± 1 min), t(10) = -6.143, P<0.005, d = 1.83). The interactions and main effects of protocol and counterweight on the dependent variables are presented in Table 13. No significant interaction between the protocol type and counterweight setting was found for any of the analysed variables. The highest mean PPO (190 ± 27 W) and VO_{2peak} (41 ± 5 mL kg^{-1} min^{-1}) were elicited during the SPT_{CW10}, which represented ≈ 62 % and 82 %, respectively, of the PPO (305 ± 30 W) and VO_{2peak} (50 ± 5 mL kg^{-1} min^{-1}) attained in double-leg cycling GXT. Between SLC conditions, PPO showed main effects for protocol type ($F_{(1,10)}$=31.452, P<0.001, partial η^2= 0.759) and counterweight setting ($F_{(1,10)}$=7.792, P=0.019, partial η^2=0.438). For both CW0 and CW10, the SLC SPT showed higher PPO in relation to the corresponding GXT protocols. Similarly, both CW10 settings produced higher PPOs than the corresponding CW0. The mean PPO difference between protocols and counterweight settings was similar, 19 (95% CI, 2-11 to 15-26) W. VO_{2peak} showed only a significant main effect of protocol type ($F_{(1,10)}$=9.347, P=0.012, partial η^2=0.483). The SPT elicited in average 2 (95% CI, 1 to 4) mL kg^{-1} min^{-1} more in $VO2_{peak}$ than the GXT. A significant main effect of counterweight setting was also present on VE_{peak} ($F_{(1,10)}$=6.509, P=0.029, partial η^2=0.294). For both the SPT and GXT protocols, the CW10 elicited significantly lower VE_{peak} comparatively to CW0, with a mean difference of 10.7 (95% CI, 1.4 to 20) L min^{-1}. On the other hand, neither HR_{peak}, RER_{peak} or $BL_{1\text{-}min}$ showed main effects of protocol (P≥0.159) or counterweight type (P≥0.097). Regarding the perceptual variables, the use of a counterweight did not influence the RPE_{peak} in SLC GXTs (19 ± 1 vs. 19 ± 1, P=0.192). $Pain_{peak}$ did not show any significant main effect (P≥0.190). Contrarily, Liking score showed main effects for protocol type ($F_{(1,10)}$=38.205, P<0.001, partial η^2=0.792) and counterweight setting ($F_{(1,10)}$=93.889, P<0.001, partial η^2=0.792), with the SPT protocol and the use of CW10 producing significantly higher Liking scores (P<0.001).

Table 13 – Interactions and main effects of protocol and counterweight setting on power output, physiological and perceptual responses to single-leg cycling tests

	GXT_{CW0}	GXT_{CW10}	SPT_{CW0}	SPT_{CW10}	Interaction Protocol x CW *P*
PPO (W) *** #	162 ± 18	171 ± 17	182 ± 22	190 ± 19	0.438
HR_{peak}(beats min^{-1})	163 ± 19	167 ± 14	166 ± 14	168 ± 14	0.563
VO_{2peak} (mL kg^{-1} min^{-1}) *	38 ± 5	38 ± 5	40 ± 5	41 ± 5	0.138
RER_{peak}	1.19 ± 0.07	1.19 ± 0.08	1.21 ± 0.07	1.21 ± 0.05	0.819
VE_{peak} (L min^{-1}) *	119 ± 15	121 ± 15	132 ± 17	129 ± 17	0.290
$BL_{1\text{-}min}$ (mmol L^{-1})	9.02 ± 1.81	9.76 ± 1.91	9.66 ± 1.80	10.06 ± 0.68	0.120
$Pain_{peak}$	9 ± 1	9 + 1	8 + 1	8 + 1	0.167
Liking score *** ###	2 ± 1	4 + 1	4 + 1	6 + 1	0.192

Data are presented as mean ± SD. $BL_{1\text{-}min}$, 1min post-test blood lactate; CW, counterweight setting; GXT_{CW0}, graded exercise test without a counterweight; GXT_{CW10}, graded exercise test with a 10kg counterweight; HR_{peak}, peak heart rate; $Pain_{peak}$, maximal rate of pain; PPO, peak power output; RER_{peak}, peak respiratory exchange ratio; SPT_{CW0}, self-paced test without a counterweight; SPT_{CW10}, self-paced test with a 10kg counterweight; VE_{peak}, maximal minute ventilation; VO_{2peak}, peak oxygen uptake. *Significant main effect of protocol type. #Significant main effect of counterweight setting. One item corresponds to P<0.05 and three items corresponds to P<0.001.

VO_2 throughout the GXTs and SPTs is represented in Figure 12. As intended, VO_2 increased over time in both GXT (P<0.001, partial η^2=0.981) and SPT (P<0.001, partial η^2=0.988) protocols. The counterweight setting also had a significant main effect of VO_2 (GXT: $F_{(1,2)}$=13.711, P=0.034, partial η^2=0.820; SPT: $F_{(1,2)}$=18.771, P=0.023, partial η^2 = 0.862). During both protocols, the use of the CW10 elicited on average 4 (95% CI, 1 to 6) mL kg^{-1} min^{-1} more than the CW0. No interactions (counterweight setting x time) were found for VO_2 (P≥0.108). Power output and cadence evolution throughout the SPTs are illustrated in Figure 13A and B. The power output increased significantly over time (P<0.001, partial η^2=0.981) with both CW0 and CW10. The counterweight setting showed a trend towards a main effect of power output, although not statistically significant ($F_{(1,2)}$= 12.601, P=0.071, partial η^2=0.863). During both SPTs, the mean peak power output was reached within the first minute of the 20 RPE stage (SPT_{CW0}: 164 ± 16 W; SPT_{CW10}: 167 ± 11 W). Time and counterweight setting

were significant main effects on cadence. Cadence increased over time ($P<0.001$, partial $\eta^2=0.907$) in both SPT_{CW0} and SPT_{CW10}. The SPT_{CW0} presented the highest cadence ($P=0.004$, partial $\eta^2=0.991$). The mean difference in cadence between SPTs was 3 (95% CI, 2 to 4) rev min^{-1}.

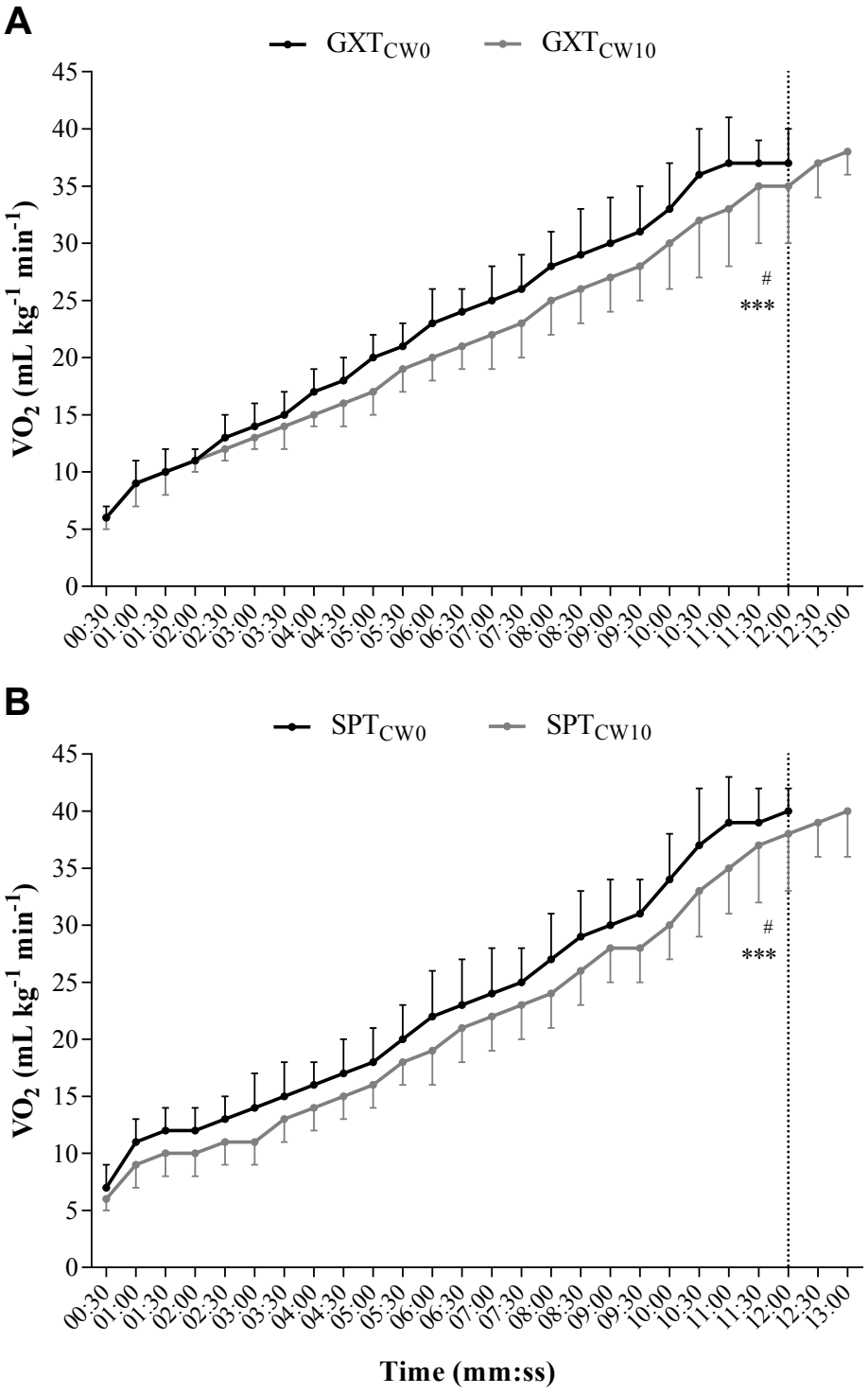

Figure 12 - The effect of the counterweight on oxygen uptake profile during single-leg cycling maximal testing

Panel A: graded exercise test without counterweight (GXT_{CW0}) vs. 10 kg counterweight (GXT_{CW10}); Panel B: self-paced protocol without counterweight (SPT_{CW0}) vs. 10 kg counterweight (SPT_{CW10}). The vertical dashed black lines represent the test duration of the GXT_{CW0} and SPT_{CW0} (mean ± SD). ***Significant main effect of time ($P<0.001$).

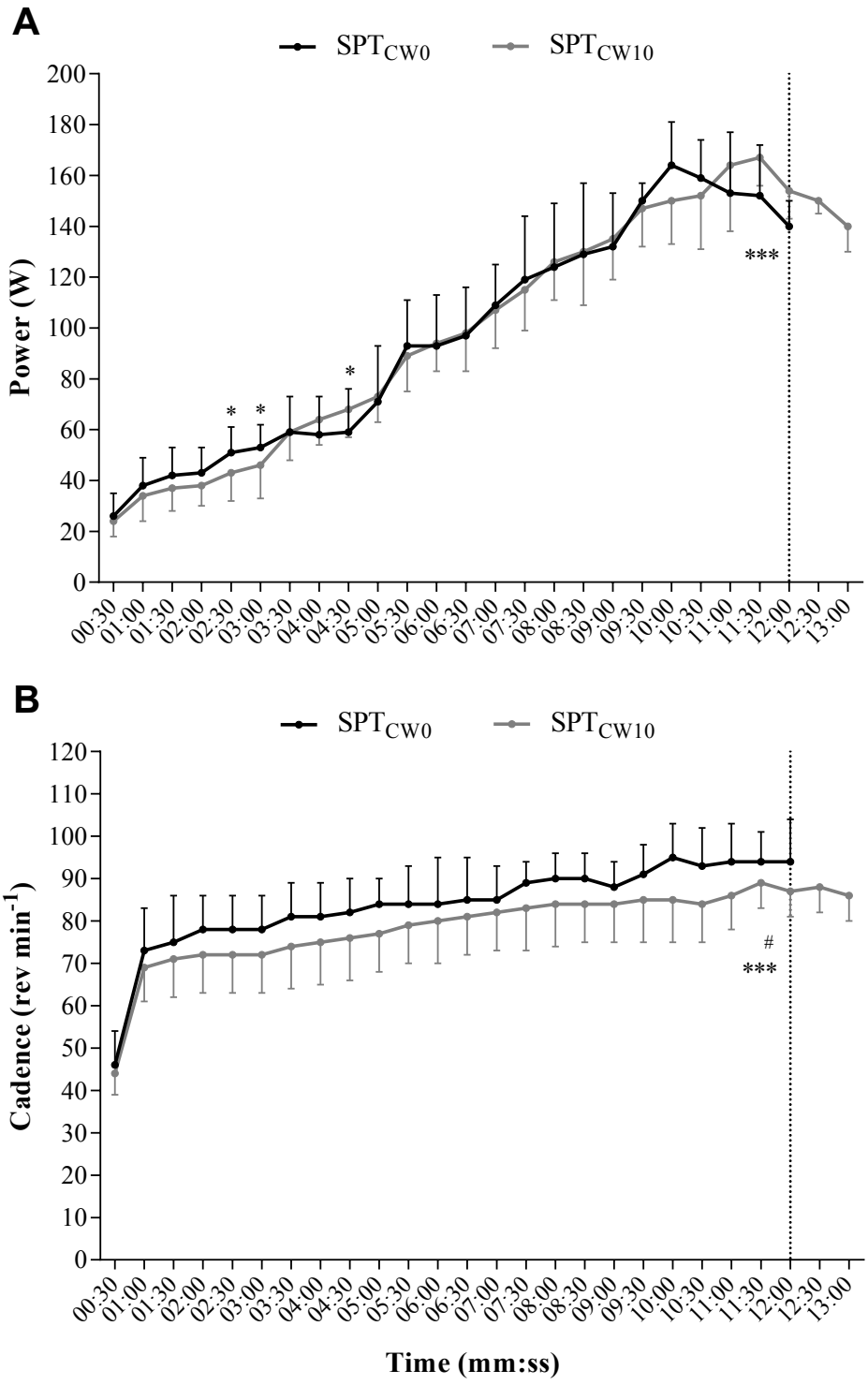

Figure 13 - The effect of the counterweight on power output and cadence profiles during single-leg cycling self-paced testing

Panel A and B illustrate the power output and cadence, respectively, during both self-paced tests without counterweight (SPT_{CW0}) and with a 10 kg counterweight (SPT_{CW10}). The vertical dashed black lines represent the test duration of SPT_{CW0} (mean ± SD). *Significant main effect of time (P<0.001). #Significant main effect of counterweight.

5. Discussion

In this study we have for the first time analysed the effect of counterweight-assisted maximal SLC exercise testing on cardiorespiratory, metabolic and perceptual responses. Furthermore, SLC testing was performed not only using a conventional GXT protocol but also through a perceptually regulated SPT. The main findings of this investigation are threefold. The first is that 10 kg counterweighted SLC may allow individuals to perform significantly longer GXTs, as well as to reach higher work rates during self-paced testing. Nevertheless, the counterweight main effect was less marked than the protocol main effect, as seen by the lower mean PPO difference between CW10 and CW0, and the relatively similar power output throughout the SPT_{CW0} and SPT_{CW10} (see Figure 13A).

For matching counterweight settings and test duration, our results showed that the PPO attained during both SPTs was ≈ 20 W higher than for the corresponding GXTs. This difference in power output between protocol types is hard to context within SLC literature. To our knowledge, no previous research using self-paced SLC has been published. A previous study from our laboratory (Thesis Part II, Chapter 2), has shown no differences in PPO between GXT and SLC protocols. However, two distinct ergometers were used in that study, and importantly, the test duration of the GXT and the SPT were different (11 ± 1 min vs. 10 ± 0 min). Thus, an absolute PPO comparison between both studies is difficult to perform. Although, similarly to the SPT_{CW0} and SPT_{CW10} in our study, the peak power output was attained at the beginning of the last stage and then followed by a subsequent drop in power output (see Figure 13A). A similar pattern was also reported in double-leg cycling research (Mauger & Sculthorpe, 2012). This is a characteristic power output variation of the SPT, which is caused by the individuals' inability to maintain the initial peak in power output at 20 RPE for the entire duration of the stage, thus a power output drop allows the subject to complete the test (Mauger & Scultorphe, 2012). Although, a study using a 7 stage SPT protocol showed a less evident drop in power output following the initial peak (Chidnok et al., 2013a) as participants attained their peak at different times during the last stage (Chidnok et al., 2013b).

The second main finding of this investigation is that peak cardiorespiratory and metabolic responses during SLC exercise testing may not be affected by the use of a 10 kg counterweight. At sub-maximal intensities, in agreement to what has been recently reported (Burns et al., 2014a), our results showed that non-counterweighted SLC elicited higher VO_2, independently of the test protocol (see Figures 12A and 12B). This higher VO_2 is possibly due to the increased recruitment of the hip flexors (Bini et al., 2015) and torso stabilising muscles during non-assisted pedal upstroke (Burns et al., 2014a; Ogita et al., 2000). Moreover, between the SPTs, the higher sub-maximal VO_2 observed during the SPT_{CW0} might also have been related with cadence. Previous research has shown that higher cadences increase oxygen demand, requiring greater oxygen delivery and greater cardiac output (Moore, Shaffrath, Casazza, & Stebbins, 2008). Nevertheless, at maximal intensities our results showed that the differences in VO_2 between CW0 and CW10 may become non-significant. Similarly, HR_{peak}, RER_{peak} and $BL_{1\text{-}min}$ were also not different between counterweight settings. The ability to perform longer SLC tests by using a CW10, might explain the similar peak responses found. Therefore, it is important to acknowledge test duration has a potential confounding factor, when comparing counterweight conditions, since it has been shown that longer-duration tests typically elicit lower VO_{2max} values (Astorino et al., 2004; Midgley, Bentley, Luttikholt, McNaughton, & Millet, 2008). However, the mean test duration difference between counterweight settings was relatively small (CW10: 12 ± 1 vs. CW0: 11 ± 1 min). Regarding the protocol type's main effect, similarly to PPO, the VO_{2peak} attained during the SPTs was significantly higher (2-3 mL kg^{-1} min^{-1}) than the GXTs. This finding is in line with the previous double-leg cycling study conducted by Mauger and Sculthorpe (2012). However, in normal cycling the ability of the SPT to elicit a higher VO_{2max} than a conventional test is debateable (Chidnok et al., 2013a; Mauger, 2013).

The last main finding of this investigation is that subjects tend to prefer counterweighted- over non-assisted SLC exercise testing. This was an expected outcome, based on previous sub-maximal SLC research (Burns et al., 2014a). Moreover, lack of enjoyment or excessive discomfort has been shown to affect negatively exercise performance and adherence (Astorino et al., 2011). Indeed, the increased coordination difficulties and peripheral discomfort of non-assisted SLC compared to normal cycling may have prevented it from becoming a mainstream exercise modality (Burns et al., 2014a). However, our results showed that the CW10 did

not result in a significant decrease in peak leg pain or perception of effort. Furthermore, for exercise testing purposes, several studies have shown that with sufficient familiarisation non-assisted SLC testing can be feasible and relatively well tolerated in different clinical populations (Bjorgen et al., 2009a; Bjorgen et al., 2009b; Olivier et al., 2010; Olivier et al., 2008; Wezenberg et al., 2012). Interestingly, our results also showed that for SLC exercise testing, subjects may prefer the SPT over a conventional incremental test, regardless of the use or not of a counterweight. Contrary to the more rigid prescriptive nature of the GXT, the SPT allows individuals to continuously adjust the power output and cadence according to their own perceived exertion, possibly making non-assisted SLC less demanding for the hip flexor muscles and more pleasant, which could be important in the clinical context, particularly following knee injury and/or surgery. Anecdotally, participants reported that cycling at higher cadences facilitated non-counterweighted SPT, which was corroborated by the cadence profile (see Figure 13B).

This investigation presents several limitations. The main limitation is the nature of the sample tested. All participants, despite having no previous experience performing SLC, were healthy and relatively young recreationally active male individuals. Thus, the results observed may not be extrapolated to general or clinical populations. Another important limitation is related to the counterweight mass used. We chose a 10 kg counterweight since the same mass was used in previous studies (Abbiss et al., 2010; Burns et al., 2014a; Elmer & Martin, 2010). These studies based their choice on pilot data (Thomas, 2009) and perceived similarity to double-leg cycling. For sub-maximal intensities, as previously mentioned, this specific counterweight mass has been shown to induce less cardiovascular stress than non-assisted SLC, and importantly, similar responses to double-leg cycling (Burns et al., 2014a). However, a recent study (Bini et al., 2015) highlighted that using a 10 kg counterweight elicits significantly different muscle recruitment and pedalling kinetics than double-leg cycling. Future investigations are needed to clarify the interaction of the counterweight mass, muscle activation and cardiorespiratory responses, considering the influence of the pedalling rate, peak power output and potentially the lower limb length and mass. For the knee rehabilitation context, the aim is to ultimately find an optimal SLC set up, possibly allowing individualised counterweight prescription. Lastly, as reported in previous research, another potential limitation could be insufficient SLC adaptation. However, we made all

efforts possible to assure that all individuals were fully familiarised with both SLC protocols.

6. Conclusion

A key finding of this study was that peak cardiorespiratory and metabolic responses to SLC exercise testing are not affected by the use of a 10 kg counterweight. This is contrary to what has been previously reported for sub-maximal intensities. Moreover, the SPT is a more palatable form of exercise, whilst eliciting similar or even higher PPO and VO_{2peak} with increased activity enjoyment, compared to conventional SLC incremental tests, regardless of the use or not of a 10 kg counterweight. Thus, perceptually regulated SLC exercise testing may be a valid alternative to conventional incremental protocols. Further studies should evaluate the use of counterweighted and non-assisted SPT protocols in clinical populations, particularly in athletes following knee injury and/or surgery.

GENERAL DISCUSSION

1. Overall Summary

Several aspects of the assessment following knee injury in physically active individuals remain unclear or have not been addressed in previous research. The general aim of the present thesis was to enhance the body of scientific knowledge, regarding both subjective and objective assessment of the knee. As a result, this thesis was structured in two distinct parts. The first part investigated the PRO measures of the knee and physical activity, specifically in terms of the instruments used following ACI procedures, as well by establishing normative KOOS scores for male marathon runners. The second part of this thesis was focused on exercise testing, particularly in assessing the potential use of the SPT concept and a counterweight device for maximal SLC exercise testing in individuals following severe knee injury and/or surgery.

PRO Measures of the Knee

The first part of this thesis comprised two separate Chapters. In Chapter 1, a systematic review was performed to assess the PRO measures that are commonly used in the evaluation of physical activity and return to sport following ACI. Not only has this systematic review been the first to specifically address ACI patients, instead of cartilage repair populations as a whole, it is one of the few published reviews on PRO measures of the knee, to provide a critical analysis of these instruments from a rehabilitative perspective. The main finding of this review was the large degree of heterogeneity between studies in the selection, but also in the timing and reporting, of patient-reported activity and return to sport scoring instruments following ACI. This

heterogeneity has been also observed in a recent systematic review conducted by Chalmers et al., (2013). However, it did not focus on ACI, as it included other cartilage repair techniques like microfracture and osteochondral autograft. Moreover, it was written from a surgical and clinical outcome perspective, rather than a rehabilitative viewpoint. In our systematic review we found that the heterogeneity in reporting physical activity does not seem to be related to study demographics or the generation of the ACI technique performed. Instead, the instrument selection is likely to be determined by individual researcher or research centre preferences. This review demonstrated that the most utilised instruments were the TAS, Lysholm Knee Functional Scale, IKDC Subjective Form and KOOS. Nevertheless, to date, the only validated instruments for a cartilage repair population are the IKDC Subjective Form and the KOOS. However, as both instruments contain similar items and provide a measure of overall function and knee symptoms, there is potential overlap between them. The IKDC Subjective Form is a single-index score consisting of 18 items developed to measure symptoms, function and sports activities in patients who have one or more knee conditions. Although, only one item is related to sports activities, which may represent an important limitation of this instrument, when assessing young and athletic individuals, including those who have undergone ACI surgery. In fact, this limitation may be one of the reasons for why none of the included studies in this review used the IKDC Subjective Form in isolation. Most of the studies analysed applied the IKDC Subjective form together with the TAS. However, it important to acknowledge that the IKDC may be associated with a better overall measure of symptoms and disabilities following articular cartilage repair. A comparative study between both instruments, conducted by Hambly and Griva (2010), has shown that the IKDC contain more items that are frequently experienced and important for this specific population.

Contrary to the IKDC, the KOOS was used independently in several of the studies included. The differentiated subscales scores provided by the KOOS, reflecting different dimensions of symptoms and function, including a function in sport and recreation subscale, is a comparative advantage of this instrument, since they allow for enhanced clinical interpretation and sensitivity to different interventions. Furthermore, the sport and quality of life related subscale scores makes the KOOS more suitable to younger and more physically active populations. Nevertheless, this review highlighted that neither the IKDC, nor the KOOS, or any of the other analysed instruments, fulfil the rehabilitation needs in the evaluation of physical activity and sports participation in

a physically active population. Specifically, the available instruments do not effectively assess the quantity and the quality of the physical activity and sports participation, as well as failing to recognise functional impairments that may be clinically relevant within the rehabilitation process. Since ACI is recommended for younger active individuals with articular cartilage defects of the knee, and return to sports is one of the main reasons for electing to undergo this particular surgery, future studies need to develop and validate patient-reported instruments that are more suited to this specific population.

Despite the aforementioned limitations in reporting physical activity and return to sport, the KOOS has already shown adequate psychometric properties not only for a cartilage repair population but also for multiple other rheumatologic and orthopaedic conditions. Importantly, this instrument is a commonly used PRO measure in athletes with knee injury (Hoch et al., 2015; Salavati et al., 2011). However, in the literature normative reference KOOS subscales scores for athletic populations were limited to football players (Frobel et al., 2008), young individuals entering the military service (Cameron et al., 2013) and downhill runners (Roi et al., 2015). Despite the high prevalence of knee RRI amongst marathon runners, no reference KOOS scores are available for this population. Therefore, in Chapter 2, we conducted an experimental study to provide normative KOOS subscales scores for a population of recreational male marathon runners. This study presents KOOS subscales values stratified by age group and history of RRI. Moreover, it demonstrated that independently of age group, runners with a knee RRI had significantly lower scores in all subscales compared to non-injured counterparts. We suggested that the magnitude of the KOOS subscales scores difference between knee RRI status observed, may mirror not only the severity of the injury, but also reflect the impact of ceiling effects observed in non-injured runners. This study, also revealed that in runners with no history of knee RRI, the KOOS subscales values may not be related to age. Despite the methodological differences between studies, particularly in the defining criteria for injury and the recall period considered, a similar trend has been shown for the other athletic populations. Furthermore, the present study demonstrated that marathon runners without knee injury from older age groups are likely to have higher KOOS subscales scores comparatively to general population. This difference might be partially explained by the fact that the reference population-based KOOS values considered (Paradowsky et al., 2006) did not account for physical activity level and more importantly, history of knee injury.

However, these are the only population-based normative values available for the KOOS. The reference KOOS subscales scores provided in Chapter 2, could be used in the future as benchmarks for rehabilitation goal setting and assessment treatment outcomes in long-distance runners with knee injury.

SLC Exercise Testing

The second part of this thesis encompassed three separate Chapters regarding SLC exercise testing. Chapters 1 and 2 aimed to assess the reliability and validity, respectively, of a perceptually regulated 5x2 min stages SPT protocol, for SLC exercise testing. These studies are original, as this was the first time the SPT concept has been applied in the SLC exercise testing context. To our knowledge, all SLC studies previously published have used GXT protocols. The 5x2 min stages SPT protocol was developed by Mauger and Sculthorpe (2012) and was used because of its shorter duration, closed-loop design and the individually orientated subjective intensities. These characteristics may elicit lower peripheral discomfort, which could be valuable for SLC exercise testing, especially with clinical populations. Moreover, previous research conducted in normal double leg cycling and treadmill running exercise testing reported the potential of the SPT to elicit higher VO_{2ma} values than conventional incremental tests (Hogg et al., 2015; Mauger et al., 2013; Mauger & Sculthorpe, 2012).

Chapter 1 study demonstrated that for SLC exercise testing, the SPT protocol elicits reliable physiological responses. All analysed variables, both peak and submaximal, including power output, were not different between sessions. Furthermore, the SPT showed both adequate relative and absolute reliability, as seen in the ICC, SEm and the Bland-Altman plots analysis. The absolute reliability of the SPT compared relatively well with previous research. Although, this comparison should be interpreted with caution, since only one study has reported reliability data for SLC exercise testing (McPhee et al., 2010) and the same occurred for the SPT concept research (Mauger et al., 2013). Importantly, both studies only provided CV data. Another relevant finding of this study was the power output pattern throughout the SPT, specifically the peak in power output observed at the beginning of the last stage and the subsequent sharp drop

until the test termination. This pattern mimics what has been observed in the original study on double-leg cycling from Mauger and Scultorphe (2012). The explanation for this pattern may be on the subjects' inability to maintain the initial peak in power output at 20 RPE for the entire duration of the stage, thus a power output drop allows the subject to complete the test.

After demonstrating the reliability of the 5x2 min stages SPT protocol for SLC exercise testing purposes, the Chapter 2 experimental study was conducted to examine the validity of the same protocol, through a concurrent comparison against a conventional fixed power incremental SLC exercise testing protocol. This study demonstrated that the SPT provides a valid means for assessing peak aerobic capacity in SLC exercise testing. No differences between SLC protocols were observed either in PPO, VO_{2peak} or in any of the other cardiorespiratory and metabolic variables analysed. The power output pattern throughout the test was similar to the pattern observed in Chapter 1 and previously described. From a clinical perspective, one of the key findings of this study was the increased activity enjoyment of the SPT compared to conventional incremental testing when performing SLC exercise testing. Alongside with the validity of the physiological responses that were seen, this finding reinforces the use of perceptually regulated protocols for this exercise testing modality. Despite its merits, this study presented some limitations that need to be acknowledge, in particular the differences regarding the ergometer used and in mean test duration between protocols. Previous research has been shown that longer-duration tests are associated with lower VO_{2max} values (Astorino et al., 2004; Midgley, Bentley, Luttikholt, McNaughton, & Millet, 2008). However, it is important to highlight that the mean difference in test duration between SLC protocols was 1 min. Additionally, in common with the Chapter 1 reliability study, another potential limitation of this investigation was the non-usage of an assisting system to help the pull phase of the pedalling cycle.

Therefore, the experimental study conducted in Chapter 3 aimed to address the limitations identified in Chapter 1 and 2 studies. Chapter 3 analysed the effect of a 10 kg counterweight on cardiorespiratory, metabolic and perceptual responses in SLC exercise testing. The GXT and SPT protocols were performed on the same electronically-braked cycle ergometer and instead of a fixed 10 min duration for the SPT, as performed in Chapters 1 and 2, its duration was individualised according to the GXT duration for the corresponding counterweight condition. In contrast to what has been previously reported for sub-maximal intensities by Burns et al. (2014a), the

findings of Chapter 3 demonstrated that peak cardiorespiratory and metabolic responses to SLC exercise testing may not be affected by the use of a 10 kg counterweight, despite an increase in the activity enjoyment. It is proposed that the ability to perform longer SLC tests by using a 10 kg counterweight possibly compensates the increased muscle recruitment of non-assisted SLC, thus explaining the analogous peak cardiorespiratory and metabolic responses responses that were found.

Furthermore, the Chapter 3 study demonstrated that compared to a GXT the SPT may generate higher peak work rates and elicit greater VO_{2peak} with increased activity satisfaction, regardless of the counterweight setting. These differences in peak responses between protocols are not in line with the Chapter 2 validity study findings for non-assisted SLC. However, the aforementioned ergometer and test duration differences are likely to explain this disparity. Interestingly, despite subjects tending to prefer counterweighted- over non-assisted SLC exercise testing, the Chapter 3 study indicated that the perceptually regulated nature of the SPT, makes non-assisted SLC possibly less demanding for the hip flexor muscles and less unpleasant relative to non-assisted conventional testing. A potential limitation of this study was the counterweight mass used. The 10 kg counterweight was chosen based on previous sub-maximal SLC research (Abbiss et al., 2010; Burns et al., 2014a; Elmer & Martin, 2010). This specific mass has shown to induce less cardiovascular stress than non-assisted SLC and similar cardiovascular responses to double-leg cycling (Burns et al., 2014a). Nevertheless, a recent study from Bini et al. (2015) highlighted that using a 10 kg counterweight elicits significantly different muscle recruitment and pedalling kinetics than double-leg cycling.

2. Conclusion and Perspectives

In conclusion, the original work of the present thesis extends the body of knowledge of two distinct, but complementary, fields in the subjective and objective knee assessment of physically active individuals. The outcomes provided from the PRO measures and the SLC exercise testing studies conducted are directly applicable to the practice of clinicians, sport rehabilitation professionals and researchers.

The review performed on reporting physical activity and return to sport is specifically relevant for ACI, but importantly, the critical analysis of the PRO instruments, is also pertinent to other knee conditions that affect physically active individuals. Furthermore, the reference KOOS subscales scores established for male marathon runners, can be an important benchmark to measure self-reported treatment outcomes in this specific population, as well as allowing comparisons with other athletic populations. Generically, future research on PRO measures should aim to develop and validate more suitable instruments to physically active individuals undergoing knee injury, that specifically acknowledge the quantity and quality of sport participation.

Regarding the original and innovative use of the SPT concept in maximal SLC exercise testing, taken together the experimental studies conducted, demonstrated that in healthy individuals, the SPT provides a reliable and valid means to assess peak aerobic fitness with increased activity enjoyment. Moreover, contrarily to what has been shown for submaximal SLC exercise, the use of a 10 kg counterweight does not seem to affect peak physiological responses. Thus, following these initial steps, future research should introduce the SPT concept into the clinical SLC exercise setting. This could be particularly relevant for athletes throughout knee rehabilitation. Additional research should also clarify the interaction between the counterweight mass, muscle activation, and cardiorespiratory responses for both submaximal and maximal SLC exercise. Ultimately, aiming to find an optimal SLC exercise testing set up and potentially allowing counterweight individualisation.

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APPENDICES

RPE scale verbal instructions before the self-paced test

‘‘You are about to undergo a self-paced single-leg cycling maximal test. The scale you see before you contains numbers from 6 to 20 this will help you adjust the exercise intensity to certain levels that I will prescribe for you. I will ask you to exercise at five intensities: 11, 13, 15, 17, and 20, in that order for 2 min at each level. For each of these ratings of perceived exertion, you will increase or decrease the intensity by altering the resistance or cadence, or both the resistance and the cadence.

“You can see on the scale that number 6 is an intensity that means no exertion at all, whilst number 20 means maximal exertion. The numbers in between these extremes represent different levels of effort. For example, a rating of 11 means a light effort, which should be the same when you are cycling with low resistance for a few minutes. A rating of 13 means the exercise is getting somewhat hard, but it still feels OK for you to continue at this level of exertion. At number 15 the exercise should be hard. Number 17 means exercise that is very strenuous. At this level, you can still go on, but you really have to push yourself as it feels very heavy and you are very tired. A rating of 19 is an extremely strenuous exercise level, this should be the same during a maximally exhaustive cycling. Please look at the scale and familiarize yourself with the numbers and words”.

“When we are ready to begin, I’ll ask you to exercise at a level that matches a rating of 11 on the scale for 2 min. Please focus on your overall feelings, not just your legs or breathing. After this first bout, you will then be asked to adjust the intensity to match a rating of 13 for a further 2 min. This will be followed by two further bouts of 2 min at 15 and 17 on the scale. The last 2 min will be at 20, your maximal exertion. Do not forget, you may continuously adjust the intensity throughout the test.”

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SYSTEMATIC REVIEW

Measuring Physical Activity and Sports Participation After Autologous Cartilage Implantation: A Systematic Review

Andre Filipe Santos-Magalhaes and Karen Hambly

Context: The assessment of physical activity and return to sport and exercise activities is an important component in the overall evaluation of outcome after autologous cartilage implantation (ACI). ***Objective:*** To identify the patient-report instruments that are commonly used in the evaluation of physical activity and return to sport after ACI and provide a critical analysis of these instruments from a rehabilitative perspective. ***Evidence Acquisition:*** A computerized search was performed in January 2013 and repeated in March 2013. Criteria for inclusion required that studies (1) be written in English and published between 1994 and 2013; (2) be clinical studies where knee ACI cartilage repair was the primary treatment, or comparison studies between ACI and other techniques or between different ACI generations; (3) report postoperative physical activity and sport participation outcomes results, and (4) have evidence level of I–III. ***Evidence Synthesis:*** Twenty-six studies fulfilled the inclusion criteria. Three physical activity scales were identified: the Tegner Activity Scale, Modified Baecke Questionnaire, and Activity Rating Scale. Five knee-specific instruments were identified: the Lysholm Knee Function Scale, International Knee Documentation Committee Score Subjective Form, Knee Injury and Osteoarthritis Outcome Score, Modified Cincinnati Knee Score, and Stanmore-Bentley Functional Score. ***Conclusions:*** Considerable heterogeneity exists in the reporting of physical activity and sports participation after ACI. Current instruments do not fulfill the rehabilitative needs in the evaluation of physical activity and sports participation. The validated instruments fail in the assessment of frequency, intensity, and duration of sports participation.

Keywords: cartilage repair, patient-report, activity-related, outcomes

Acute and chronic articular cartilage lesions can lead to severe limitation of physical activity and sports participation and an increased risk of early degenerative changes and disability.[1–3] The prevalence of articular cartilage lesions is often higher in individuals who participate in sports activities.[4] These lesions affect not only high-level competitive athletes[5,6] but also recreational athletes, especially those involved in pivoting sports.[7] Autologous chondrocyte implantation (ACI) is a chondrocyte-based surgical technique developed in Sweden in the 1980s for the treatment of cartilage injuries.[8] Since the first published clinical study in 1994,[9] several different generations of the ACI technique have been developed.[10–13] ACI is proposed to be the preferred treatment option for younger active patients with large articular cartilage defects, short duration of symptoms, and no previous cartilage surgery.[14] The assessment of physical activity and sports engagement is extremely important after ACI since return to sports and exercise activity is one of the main reasons for electing to undergo ACI,[15] and for many patients the goal is to return to a preinjury sports level.[7,16,17] Self-report physical activity questionnaires or interviews are commonly used to measure physical activity and sports participation.[18] There is currently no agreement regarding a gold-standard patient-assessed measure to follow up the effects of a cartilage-repair surgery.[19] For ACI patients or for cartilage-repair patients as a whole, there are no disease- or population-specific self-reported outcomes. The instruments that have been applied to measure physical activity in this population were originally developed for other knee injuries. Moreover, only 2 instruments, the International Knee Documentation Committee Score (IKDC) Subjective Form and the Knee Injury and Osteoarthritis Outcome Score (KOOS) are currently validated for a cartilage-repair population,[20,21] but not specifically for ACI patients. There is a potential overlap between these instruments, since both provide an overall score of the patient's perception of the knee. The discrepancies on reporting physical activity and sports participation after ACI seen in the literature make the understanding and the usefulness of these instruments unclear.

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Objectives

The objectives of this review were to identify the patient-report instruments that are commonly used in the evaluation of physical activity and return to sport after ACI and provide a critical analysis of these instruments from a rehabilitative perspective.

Evidence Acquisition

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[22] and the *Cochrane Handbook for Systematic Reviews*.[23]

Search Strategy

The electronic search was undertaken independently by both authors in January 2013 and repeated in March 2013 for validation. The following databases were used: PubMed (MEDLINE), Cochrane Central Register of Controlled Trials, Cumulative Index for Nursing and Allied Health Literature (CINAHL), SPORTDiscus, and Physiotherapy Evidence Database (PEDro). The electronic search strategy used was (((*physical activity* or *sport** or *functional* or *activity scale* or *sports scale* or *activity rating* or *sports rating*) and (*knee* or *knee injury* or *knee surgery*)) and (*cartilage repair* or *chondral repair* or *chondrocyte implantation* or *chondrocyte transplantation* or *MACI* or *MACT* or *ACI* or *CACI* or *PACI* or *CCI* or *ACT* or *AMIC* or *Hyalograft C* or *CaRes*)). The search period was from January 1, 1994, to March 1, 2013. All searches were carried out with the following inclusion criteria:

- English-language clinical studies published between 1994 and 2013
- Studies where the primary knee surgical treatment was ACI cartilage repair without any other concomitant surgeries
- Comparison studies of any generation of ACI with any cartilage-repair or -restoration technique
- Comparison studies of any generation of ACI with a different generation of ACI
- Studies reporting postoperative physical activity and sport participation outcomes results
- Therapeutic-type studies with level of evidence of I, II, or III according to Oxford Centre for Evidence-Based Medicine[24]

The exclusion criteria were

- Non-English-language studies
- Review studies
- In vitro, animal, and nonclinical studies
- Studies where the ACI procedure was not performed
- Studies reporting data exclusively from ACI procedures in the patellofemoral joint
- Studies with osteoarthritic populations

Study Selection

A process of study selection was implemented across all studies resulting from the search strategy. First, all duplicates, review studies, and articles not in the English language were excluded. The abstracts of the remaining citations were then reviewed for potential eligibility against the inclusion and exclusion criteria. In cases in which the abstracts did not give full information about the inclusion criteria for this review, the full-text versions of the studies were reviewed. After review of the full-text articles, studies that met the inclusion criteria were included in the systematic review. All studies identified were independently reviewed by both researchers and checked for potentially inclusive references. The first author was responsible for the final inclusion or exclusion decision in case of disagreement. In addition, reference lists of relevant studies were reviewed to identify studies not found through the primary electronic searches.

Quality Assessment

The quality of the studies as previously referred to in the inclusion criteria was assessed by both researchers using the Oxford Centre for Evidence-Based Medicine.[24] The evidence levels for each study were assigned after determining the primary research question and establishing the study type. Only therapeutic-type studies with levels of evidence of I to III were included

Data Extraction

The data from the selected studies were extracted and compiled in tabular form by both authors. The data extracted from each eligible study included surgical procedure, maximum follow-up and intermediate assessments, demographics (number of patients, gender, and age), and the self-report physical activity and sport participation instruments used at each assessment.

Evidence Synthesis

Study Selection

The initial search of all databases used yielded 721 citations. The flowchart in Figure 1 summarizes the selection-process algorithm via PRISMA guidelines.[22] After the removal of duplicates; reviews; non-English, in vitro, animal, and nonclinical papers; and studies reporting non-ACI cartilage techniques, 74 studies were included for possible review. After the review of the full text of their abstracts, 3 studies reporting patellofemoral-joint ACI and 1 study in an osteoarthritic population were removed, and 46 studies were removed since the evidence level provided was >III. The remaining list of studies was cross-checked against the reference lists of relevant studies, and 2 studies[25,26] that were not found in the electronic search were included in the final studies list. At the end, after the application of all inclusion and exclusion criteria, 26 studies[25–50] were selected for

this review. Three of these studies[28,34,37] used the same population as early studies.[27,35,38] However, they were included since they reported different follow-up periods.

Data Synthesis

Included Studies' Characteristics. The main characteristics of the selected studies are presented in Table 1. There was a wide range of variation in patient demographics across all the 26 included studies. The age ranged from 15 to 62 years. The overall number of patients, excluding the studies with the same patient cohort, was 1595; the number of patients in each study ranged from 19 to 154; and there was a predominance of male gender in all studies, although 4 studies[43–45,49] did not report gender distribution. In terms of levels of evidence, 2 studies[33,44] were classified as evidence level III, 14 studies* as level II, and 10 studies† as level I.

*References 25, 26, 28–30, 35, 39–43, 47, 49, 50.
†References 27, 31, 32, 34, 36–38, 45, 46, 48.

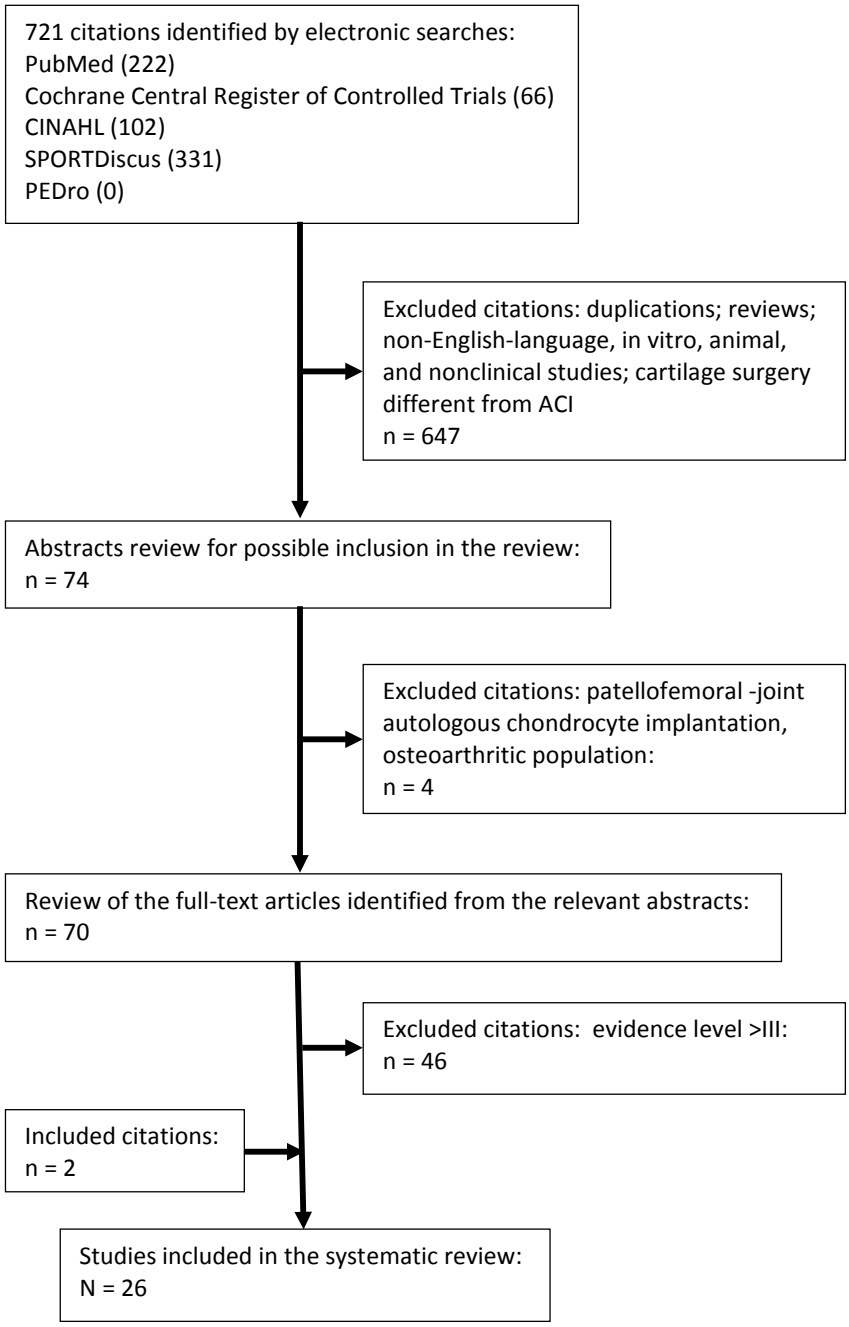

Figure 1 — Flow diagram reporting the process of study selection.

Table 1 Surgical and Demographic Overview of Included Studies

Study	Evidence level	Surgical intervention	Mean follow-up	Demographics		
				N	Gender (male/female)	Mean age, y (range)
Bassad et al[31]	I	MACI	24 mo	40	25/15	33.0
		MF		20	17/3	37.5
Bentley et al[28]	II	ACI	10 y	58	33/25	30.9 (16–49)
		MF		42	27/15	31.6 (20–48)
Bentley et al[27]	I	Mosaicplasty	1 y	42	27/15	31.6 (20–48)
		ACI		58	33/25	30.9 (16–49)
Cole et al[29]	II	MF	24 mo	9	5/4	33.1 ± 10.1
		CAIS		20	14/6	32.7 ± 8.8
Della Villa et al[33]	III	ACI—hyalograft C (intensive RB athletes)	5 y	31	31/0	23.5 ± 5.7
		ACI—hyalograft C (normal RB nonathletes)		34	34/0	25.1 ± 5.8
Dozin et al[25]	II	ACI	291 d[a]	22	17/5	29.61 ± 7.31
		Mosaicplasty	300 d[a]	22	10/12	27.89 ± 8.08
Ebert et al[34]	I	MACI (accelerated WB)	5 y	31	20/11	36.8 (21–62)
		MACI (normal WB)		32	21/11	39.6 (16–63)
Ebert et al[35]	II	MACI (accelerated RB)	3 mo	31	20/11	36.9 (21–62)
		MACI (traditional RB)		31	20/11	39.7 (16–60
Gooding et al[36]	I	PACI	2 y	33	NR	30.52(15–52)
		CACI		33	NR	30.54 (16–49)
Horas et al[26]	II	ACI	24 mo	20	8/12	31.4 (18–42)
		Osteochondral cylinder		20	15/5	35.4 (21–44)
Knutsen et al[37]	I	ACI	5 y	40	NR	33.3
		MF		40	NR	31.1
Knutsen et al[38]	I	ACI	2 y	40	NR	33.3
		MF		40	NR	31.1
Kon et al[30]	II	MF (football players)	7.5 y	20	20/0	26.5 (18–35)
		ACI (football players)		21	21/0	23.7 (16–37)
Kon et al[39]	II	MF	5 y	40	27/13	30.6
		ACI—hyalograft C		40	33/7	29.0
Kreuz et al[40]	II	ACI (athletes)	36 mo	69	44/25	34.97 (18–50)
		ACI (nonathletes)		49	25/24	36.25 (18–50)
Lim et al[41]	II	MF	5 y	30	17/13	32.9 (30–45)
		OAT		22	12/10	30.4 (20–39)
		ACI		18	10/8	25.1 (18–32)
Niemeyer et al[42]	II	MACI (age >40 y)	24 mo	37	NR	44.76 ± 4.53
		MACI (age ≤ 40 y)		37	NR	31.05 ± 6.14
Panagopoulos et al[43]	II	PACI or MACI (athletes/soldiers)	37.5 mo	19	15/4	32.2 (18–43)
Pestka et al[44]	III	ACI (after failed MF)	48 mo	28	16/12	34.1 ± 9
		ACI	41.4 mo	28	16/12	33.6 ± 10.1
Saris et al[32]	I	CCI	36 mo	57	35/22	33.9 ± 8.5
		MF		61	41/20	33.9 ± 8.5
Van Assche et al[45]	I	ACI	2 y	33	22/11	31 ± 8
		MF		34	24/19	31 ± 8
Vanlauwe et al[46]	I	CCI (symptoms <3 y)	60 mo	34	71% male	33.3 (18–50)
		MF (symptoms <3 y)		39	72% male	33.9 (20–50)
		CCI (symptoms ≥ 3 y)		17	47% male	34.2 (19–47)
		MF (symptoms ≥ 3 y)		22	59% male	33.9 (18–50)
Visna et al[47]	II	ACI	12 mo	25	18/7	29.48(18–50)
		Abrasive techniques		25	16/9	32.20 (21–50)
Wondrasch et al[48]	I	ACI (accelerated WB)	104 wk	16	12/4	28.3 (18–53)
		ACI (delayed WB)		15	11/4	33.0 (18–55)
Zaslav et al[49]	II	ACI (after failed prior surgery)	48 mo	154	106/0	34.5 ± 8.1
Zeifang et al[50]	II	ACI (periosteal)	24 mo	10	10/0	29.1 ± 7.5
		MACI		11	6/5	29.5 ± 11.0

Abbreviations: ACI, autologous chondrocyte implantation; CACI, collagen membrane cover ACI; CAIS, cartilage autograft implantation system; CCI, characterized chondrocyte implantation; MACI, matrix-induced ACI; MF, microfracture; NR, not reported; OAT, osteochondral autograft transplantation; PACI, periosteal cover ACI; RB, rehabilitation; WB, weight bearing.
[a] Median.

Fifteen studies were randomized controlled trials,‡ of which nine[27,31,32,36–38,45,46,48] were categorized as evidence level I studies. Regarding the surgical interventions, 11 studies[33–36,40,42–44,48–50] reported data exclusively from ACI techniques; the remaining studies compared ACI techniques with other techniques such as abrasive techniques,[47] microfracture and/or osteochondral autograft transplantation,[28–32,37–39,41,45,46] and mosaicplasty.[27,46] The studies performed predominantly first-generation ACI techniques; 2 studies[36,43] included second-generation ACI, and 6 studies[31,34,35,42,43,50] performed third-generation ACI. Concerning the rehabilitation process, 3 studies[34,35,48] distinguished accelerated from delayed weight bearing after ACI, and 1 study[33] compared intensive rehabilitation in athletes with normal rehabilitation in nonathletes. Four studies[30,33,40,43] reported data from competitive athletes; in one[30] the patient sample was composed only of competitive football players.

Patient-Report Instruments. The self-report instruments used in each study at each assessment are described in Table 2. The majority of the studies reported multiple assessments with a mean follow-up of 38.6 months. Four studies[33,34,37,39,41] reported mean follow-up periods of 5 years, 1 study[30] reported 7.5 years, and another study,[28] 10 years. However, the majority of the studies only reported mean assessment time and did not report the minimum and maximum assessment time. Where studies did report the range of time scales about the mean assessment time, a wide range of variation was found.[25,27,41,43,44] The self-report physical activity and sports participation instruments used in these studies were the Tegner Activity Scale (TAS), the Modified Baecke Questionnaire, and the Activity Rating Scale. The knee-specific instruments used were Lysholm Knee Function Scale, the International Knee documentation Committee Score (IKDC) Subjective Form, the Knee Injury and Osteoarthritis Outcome Score (KOOS), the Modified Cincinnati Knee Score, and the Stanmore-Bentley Functional Score; the only general health questionnaire applied was the Short Form-36 Health Survey. The main characteristics of each of these instruments are presented in Table 3. The most-used instruments were the TAS (13 studies), Lysholm scale (10 studies), IKDC Subjective Form (10 studies), and KOOS (8 studies). Two studies[30,39] reported the preinjury TAS. The Lysholm scale was applied together with the IKDC Subjective Form in 5 studies,[25,42,43,47,50] but no studies used the Lysholm scale in conjunction with the KOOS. Three studies applied both the IKDC and KOOS.[29,44,48] Regarding the less-used instruments, the Modified Cincinnati Knee Score was applied in 6 studies,[27,28,36,40,42,49] the Short Form-36 Health Survey was used in 5 studies,[29,34,35,37,38] the Activity Rating Scale and its modified version in 2 studies,[44,45] and only 1 study[45] applied the Modified Baecke Questionnaire.

‡References 25–29, 31, 32, 36–38, 45–48, 50.

Discussion

This was the first systematic review to specifically evaluate the use of patient-reported-activity scoring instruments after ACI from a rehabilitative perspective. Previous reviews have been published for patient-based instruments for the knee in general[51–54] and for other specific knee disorders.[55,56] Recently Chalmers et al[57] published a review of activity-related outcomes for articular cartilage repair, but it was written from a surgical and clinical outcome perspective, rather than rehabilitative, and did not focus specifically on ACI.

The first finding of this review was the wide range of variation in the studies' demographics in relation to patient numbers (19–154), age (15–62 y), and postoperative reporting time points (3–83.6 mo). Note that it was not only the selection of study time points that varied but also the range in data-collection times about those points, which in some instances was up to 5 years.[41,44] However, the majority of the studies did not report these range values. These inconsistences in reporting are pertinent to rehabilitation, as it is a time-based process. It is recommended that researchers consider reporting the range in postoperative times alongside the mean time for patient-reported outcome evaluations. The main finding from this review was the large degree of heterogeneity between studies in the use of patient-report instruments to evaluate physical activity and return to sport. This was observed not only in the selection of an individual instrument but also within the set or group of instruments applied, particularly the combinations of physical activity scales, knee-specific instruments, and general health questionnaires. This heterogeneity in reporting physical activity does not seem to be related to study demographics or the generation of the ACI technique that is performed. Instrument selection is more likely to be determined by individual researcher or research center preferences for particular instruments. The use of a particular set of instruments at a center does allow for intracenter comparison, but the variation in the selection of physical activity scales and knee-specific instruments between centers makes intercenter comparisons problematic.

As reported in the results, the most-used instruments were the TAS, Lysholm scale, IKDC Subjective Form, and KOOS. The higher prevalence of TAS is not a surprise, since it is the most widely used activity-scoring system for patients with knee disorders.[58] The TAS is a single-item instrument designed as a score of activity level to complement the Lysholm scale for patients with ligamentous injuries.[59,60] Despite generally demonstrating acceptable psychometric parameters,[61] neither the TAS nor the Lysholm scale have been validated for the cartilage-repair population. The TAS scores a person's activity level on a scale of 0 to 10 where 0 is *on sick leave/disability* and 10 is *participation in competitive sports such as soccer at a national or international elite level*.[59] In spite of the possible advantage of retrospective assessment, from a rehabilitation perspective, there are significant limitations in using the TAS.

Table 2 Summary of Patient-Reported Instruments Used in Each Study

Study	Assessment time points (range)	LKFS	IKDC	KOOS	TAS	M-CKS	SF-36	ARS	M-Baecke	S-B
Bassad et al[31]	Presurgery	X			X					
	3 mo	X								
	6 mo	X			X					
	12 mo	X			X					
	18 mo	X								
	24 mo	X			X					
Bentley et al[28]	Presurgery					NR				NR
	≥10 y					X				X
Bentley et al[27]	Presurgery					NR				NR
	19 mo (12–26)					X				X
Cole et al[29]	Presurgery		Graph	Graph			Graph			
	6 mo		Graph	Graph			Graph			
	12 mo		X	X			Graph			
	18 mo		Graph	Graph			Graph			
	24 mo		X	X			Graph			
Della Villa et al[33]	Presurgery		X		X					
	12 mo		X							
	24 mo				X					
	5 y		X		X					
Dozin et al[25]	Presurgery	X	NR							
	Mosaicoplasty group									
	291 d[a] (0–1339)	X	NR							
	ACI group									
	300 d[a] (0–994)	X	NR							
Ebert et al[34]	Presurgery			X			X			
	3, 6, 12, 24 mo			X			X			
	5 y			X			X			
Ebert et al[35]	Presurgery			X			X			
	3 mo			X			X			
Gooding et al[36]	Presurgery					X				
	24 mo					X				
Horas et al[26]	Presurgery	Graph			Graph					
	6,12, 24 mo	Graph			Graph					
Knutsen et al[37]	Presurgery	Graph			X		Graph			
	12, 24 mo	Graph			NR		Graph			
	5 y	Graph			X		Graph			
Knutsen et al[38]	Presurgery	Graph			NR		Graph			
	12, 24 mo	Graph			NR		Graph			
Kon et al[30]	Preinjury				X					
	Presurgery		X		X					
	24 mo		X		X					
	7.5 y		X		X					
Kon et al[39]	Preinjury				X					
	Presurgery		X		X					
	24 mo		X		X					
	5 y		X		X					
Kreuz et al[40]	Presurgery					X				
	6,18, 36 mo					X				
Lim et al[41]	Presurgery	X			X					
	1, 6, 12, 24, 36 mo	X			X					
	5 y (3–10)	X			X					
Niemeyer et al[42]	Presurgery	X	X		X	X				
	6, 12 mo	Graph	X		NR	NR				
	24 mo	X	X		X	X				
Panagopoulos et al[43]	Presurgery	X	X		X					
	3, 6, 12, 36 mo	Graph	Graph		Graph					
	37.5 mo (36-42)	X	X		X					

(continued)

Table 2 (*continued*)

Study	Assessment time points (range)	LKFS	IKDC	KOOS	TAS	M-CKS	SF-36	ARS	M-Baecke	S-B
Pestka et al[44]	Presurgery							X[b]		
	ACI (failed MF) group									
	48 mo (15.1–75.1)		X	X				X[b]		
	ACI group									
	41.4 (15.4–83.6)		X	X				X[b]		
Saris et al[32]	Presurgery			Graph						
	6, 12, 24 mo			Graph						
	3 y			X						
Van Assche et al[45]	Preinjury							X		
	Presurgery							X		
	12 mo							X		
	24 mo							X	X	
Vanlauwe et al[46]	Presurgery			X						
	12, 24 mo			Graph						
	36, 48 mo			Graph						
	60 mo			X						
Visna et al[47]	Preinjury				X					
	Presurgery	X	X		X					
	5 mo	X	X		NR					
	12 mo	X	X		X					
Wondrasch et al[48]	Presurgery		Graph	Graph	Graph					
	4, 12, 24, 52 wk		Graph	Graph	Graph					
	104 weeks		X	X	X					
Zaslav et al[49]	Presurgery			X		X				
	6, 12, 24, 36, 48 mo			X		X				
Zeifang et al[50]	Presurgery	X	X		X					
	3, 6 mo	NR	NR		X					
	12, 24 mo	X	X		X					

Abbreviations: ACI, autologous chondrocyte implantation; ARS, Activity Rating Scale; IKDC, International Knee documentation Committee Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; LKFS, Lysholm Knee Function Scale; M-Baecke, Modified Baecke Questionnaire; M-CKS, Modified Cincinnati Knee Score; MF, microfracture; SF-36, Short Form-36 Health Survey; S-B, Stanmore-Bentley Functional Score; TAS, Tegner Activity Scale; NR, not reported; Graph, graphical results.
[a] Median. [b] Modified ARS.

Table 3 Main Characteristics of the Patient-Reported Instruments Used in the Studies

	Score	Number of items	Subscales or subscores	Validated or recommended for ACR
Knee-specific instruments				
M-CKS[69]	0–100	10	Sports activity; change in sports activity, function, ability to participate in sports, symptoms	Recommended[70]
IKDC Subjective Form[66]	0–100	18	Symptoms, sport activities, function	Validated[20]
KOOS[71]	0–100	42	Pain, symptoms, function in daily living activities, knee-related quality of life, function in sport and recreation	Validated[21]
LKFS[60]	0–100	8	Instability, pain, catching, locking, swelling, stair climb, squat, limp, support	No
S-B[19]	0–4	4		No
Physical activity scales				
ARS[66]	0–16	4	Running, cutting, decelerating, pivoting	No
M-Baecke[63]	0–10	10	Household, sport, leisure	No
TAS[59]	0–10	1		No
General health questionnaires				
SF-36[71]	0–100	36	Physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, physical component, scale, mental component scale	Recommended[70]

Abbreviations: ACR, articular cartilage repair; ARS, Activity Rating Scale; IKDC, International Knee Documentation Committee Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; LKFS, Lysholm Knee Function Scale; M-Baecke, Modified Baecke Questionnaire; M-CKS, Modified Cincinnati Knee Score; SF-36, Short Form-36 Health Survey; S-B, Stanmore-Bentley Functional Scale; TAS, Tegner Activity Scale.

The scale does not provide any qualitative information regarding intensity, frequency or the ability to maintain uncompensated participation at the graded activity level. The other activity-rating scales identified in this review were the Modified Baecke Questionnaire[45] and the Activity Rating Scale,[45] and also a modified Activity Rating Scale,[44] which included a lifetime sports assessment.[62] The Modified Baecke[63] is an adapted version of the physical activity questionnaire Baecke et al[64] developed for older adults. This instrument consists of 10 items, with subscores for household activities, sport activities, leisure-time activities, and sport activities. The sport-activity assessment is based on a single item that, despite taking into account frequency, is very poor in terms of the evaluation of intensity, ranging the intensity from *lying, unloaded* to a maximum of *walking, body movements, cycling, swimming.* This reflects the elderly adults for whom the instrument was developed and does not represent the average age profile of individuals who undergo ACI. The Activity Rating Scale is a 4-item scale developed specifically for knee disorders.[66] The scale grades running, cutting, decelerating, and pivoting separately and does take into account the frequency of participation for each activity. However, all the graded activities are running-related, which means that this instrument is not suitable for evaluating ACI, with which running is restricted in the early and midstages of rehabilitation.

Currently, the only validated instruments for a cartilage-repair population are the IKDC Subjective Form[20] and the KOOS.[21] These instruments have some similar items that could result in an overlap between them, especially as both provide a measure of the overall function and symptoms of the knee. Despite this potential overlap, in the current review 3 studies[20,51,55] applied both instruments together. The IKDC is a knee-specific instrument developed to measure symptoms, function, and sports activities in patients who have 1 or more of a variety of knee conditions.[66] The IKDC Subjective Form is a single-index score consisting of 18 items. However, only 1 of those items is related to the assessment of sports activities, and this represents an important limitation. This limitation may be 1 of the reasons why none of the included studies in this review used the IKDC Subjective Form independently. Most of the studies[33,39,42,43,50] applied the IKDC Subjective Form together with the TAS. The KOOS was developed from the disease-specific Western Ontario and McMaster Universities Osteoarthritis Index.[67] The KOOS[68] consists of 42 items with 5 separately scored subscales; 1 of these subscales is "function in sport and recreation," which comprises 5 items. The KOOS's capacity of providing these differentiated subscale scores in addition to the overall score is an advantage in comparison with the IKDC, although previous research found that the IKDC Subjective Form provided a better overall measure of symptoms and disabilities that were important to individuals who had undergone articular cartilage repair.[19] When looking specifically at physical activity and sports participation after ACI, both the IKDC and the KOOS have limitations, as neither instrument evaluates the frequency, duration, and ability of a person to maintain the intensity of the sports activity without compensations.

The other knee-specific instruments found in this review were the Stanmore-Bentley Functional Rating Score[18,19] and the Modified Cincinnati Knee Score.[18,19,43,47,49,56] The usefulness of the Stanmore-Bentley Functional Rating Score is very limited after ACI, since it is a very simplistic functional rating scale based on pain and level of activity. On the other hand, the Modified Cincinnati Knee Score (also known as the Noyes Knee Rating System) could be useful for ACI since it takes into account the intensity and the weekly frequency grading of the sports activity. The Modified Cincinnati Knee Score is composed of 10 items that are used to grade sports activity, change in sports activity, function, ability to participate in sports, and symptoms, with a score ranging from 0 to 100.[69] The use of the Modified Cincinnati Knee Score with the Short Form-36 Health Survey has been recommended for preoperative evaluation and postoperative review of all patients undergoing ACI.[70] However, this instrument is not currently validated for general cartilage-repair or ACI populations. It is curious that none of the included studies applied the Modified Cincinnati Knee Score and Short Form-36 Health Survey together.

Conclusions

Participation in physical activities, including sport and exercise, is one of the main reasons that individuals choose to undergo ACI of the knee. It is evident from this review that there is considerable heterogeneity in the selection, timing, and reporting of patient-report activity-scoring instruments after ACI, which makes a systematic comparison difficult and biases the interpretation of these outcomes. A key finding from this review was that the instruments currently used to evaluate postoperative outcomes in an articular-cartilage-repair population do not fulfill rehabilitative needs in the evaluation of physical activity and sports participation. A suitable instrument should identify not only whether an individual is able to participate in certain physical activities but also the quantity and quality of this participation. In particular from a rehabilitative perspective, the ability to recognize compensatory functional movement and factors that may indicate incomplete rehabilitation and predispose to further injury are not being elucidated from current patient-report outcome instruments. Further research is needed in the development and validation of physical activity and sports participation patient-report instruments suited to the ACI population.

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