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Case study

Muscle-tendon glucose uptake in Achilles tendon rupture and tendinopathy before and after eccentric rehabilitation: Comparative case reports

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ABSTRACT

Achilles tendon rupture (ATR) is the most common tendon rupture injury. The consequences of ATR on metabolic activity of the Achilles tendon and ankle plantarflexors are unknown. Furthermore, the effects of eccentric rehabilitation on metabolic activity patterns of Achilles tendon and ankle plantarflexors in ATR patients have not been reported thus far. We present a case study demonstrating glucose uptake (GU) in the Achilles tendon, the triceps surae, and the flexor hallucis longus of a post-surgical ATR patient before and after a 5-month eccentric rehabilitation. At baseline, three months post-surgery, all muscles and Achilles tendon displayed much higher GU in the ATR patient compared to a healthy individual despite lower plantarflexion force. After the rehabilitation, plantarflexion force increased in the operated leg while muscle GU was considerably reduced. The triceps surae muscles showed similar values to the healthy control. When compared to the healthy or a matched patient with Achilles tendon pain after 12 weeks of rehabilitation, Achilles tendon GU levels of ATR patient remained greater after the rehabilitation. Past studies have shown a shift in the metabolic fuel utilization towards glycolysis due to immobilization. Further research, combined with immuno-histological investigation, is needed to fully understand the mechanism behind excessive glucose uptake in ATR cases.

1. Introduction

Despite the substantial strength of the Achilles tendon, its rupture is the third most common tendon disorder with a rising incidence (Leppilahti, Puranen, & Orava, 1996; Lesic & Bumbasirevic, 2004; Möller, Åström, & Westlin, 1996). Although the precise pathogenesis of Achilles tendon rupture is unknown, contributing factors identified in the literature include tendon degeneration, failure of the normal inhibitory mechanism of triceps surae myotendon complex, drugs, systemic disease, genetics, foot deformity, and pre-existing Achilles tendon pathology (Leppilahti & Orava, 1998). There is a substantially increased, up to 200-fold, risk of contralateral Achilles tendon rupture in patients who have previously suffered a rupture on one side. Finally, nearly half of the patients experience post-rupture tendon problems in the long run (Årøen, Helgø, Granlund, & Bahr, 2004).

Surgical repair, despite higher costs and potential surgical complications, has been growing in popularity as the treatment of choice due to the decreased incidence of re-rupture and a faster restoration of normal function (Kader, Deehan, & Maffulli, 2007; Leppilahti & Orava, 1998). Post-operative physical rehabilitation plays a vital role in the full return to pre-rupture physical activity level and sport (Mortensen, Skov, & Jensen, 1999). Among the rehabilitation plans available is the heavy-load eccentric calf muscle training regimen proposed by Alfredson, Pietilä, Jonsson, and Lorentzon (1998). Although primarily designed for the conservative treatment of chronic Achilles tendinopathy, eccentric training can be used as a strength training procedure in Achilles tendon rupture management as well, however its efficacy has yet to be demonstrated. The beneficial effects of eccentric loading on Achilles tendon health have been well documented in humans (Fouré,

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Nordez, & Cornu, 2013; Sussmilch-Leitch, Collins, Bialocerkowski, Warden, & Crossley, 2012; Van der Plas et al., 2012). Moreover, the potential of such exercise in reversing pathological neovascularization (Öhberg & Alfredson, 2004), a pathology that is considered contentious by some, could help in tendon pain relief. However, it must be noted that slow concentric contractions have also demonstrated promise as a rehabilitation tool and should be investigated further (Kjaer & Heinemeier, 2014), as well as isometric contractions for pain relief (Rio et al., 2015).

Skeletal muscle glucose uptake is increased during exercise due to a coordinated rise in glucose delivery rate, surface membrane glucose uptake, and intracellular substrate flux through glycolysis (Rose & Richter, 2005). High-resolution positron emission tomography (PET), with [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) tracer, is an effective way of not only non-invasively investigating whole muscle metabolic activity through glucose uptake measurements (Bojsen-Møller, Losnegard, Kemppainen, Viljanen, Kalliokoski, & Hallén, 2010; Heinonen, Nesterov, Kemppainen, Fujimoto, Knuuti, & Kalliokoski, 2012; Kalliokoski et al., 2007) but also detecting inflammation (Goldsmith & Vallabhajosula, 2009). Since there is evidence of tendon inflammation present on the site of Achilles tendon rupture (Cetti, Junge, & Vyberg, 2003), FDG-PET investigation would provide significant insights into the metabolic activity of the tendon. Additionally, Achilles tendinous tissue has been demonstrated to take up glucose in response to exercise (Bojsen-Møller, Kalliokoski, Seppänen, Kjaer, & Magnusson, 2006; Masood, Kalliokoski, Bojsen-Møller, Peter Magnusson, & Finni, 2014; Masood, Kalliokoski, Magnusson, Bojsen-Møller, & Finni, 2014).

This kind of protocol has been recently applied in several other experiments (Fujimoto, Kemppainen, Kalliokoski, Nuutila, Ito, & Knuuti, 2003) and is realized by the properties of [^{18}F]-FDG that enables its entrapment in the cells. As there is some tracer still available in the plasma to be taken up by the cells after the cessation of exercise, it may affect the measure of glucose uptake during exercise. However, this effect has previously been estimated to be small (Kemppainen, Fujimoto, Kalliokoski, Viljanen, Nuutila, & Knuuti, 2002) and most probably in line with the relative usage of the muscles during the preceding exercise.

The purpose of the present study was twofold. Firstly, to compare calf myotendon glucose uptake (GU) in a post-surgically repaired complete Achilles tendon rupture (ATR) patient to that of a healthy individual (CTRL) during submaximal isometric calf muscle contraction. Secondly, to explore the effects of eccentric rehabilitation on myotendon metabolic activation in ATR patient as compared to those in an Achilles tendon pain patient. It was hypothesized that isometric exercise-induced glucose uptake rate of the operated Achilles tendon and related triceps surae muscle would be higher compared to the healthy control. Furthermore, eccentric rehabilitation would help in lowering the isometric exercise-induced glucose uptake in the ruptured Achilles tendon and triceps surae in the long-run.

2. Methods

2.1. Participants

Achilles tendon rupture (ATR): a 27-year old male with post-surgical complete mid-portion Achilles tendon rupture was evaluated. The subject was a recreational ice hockey player with a history of complete, acute left Achilles tendon rupture while playing badminton. The tendon was surgically repaired 3 months prior to the participation in the study. Before the baseline measurements the subject was cleared by the operating surgeon for full weight-bearing and did not report any other systemic or musculoskeletal disorder. His body mass and height were 79 kg and 183 cm, respectively. Both operated (OPER) and unoperated (UNOP) legs were examined in this study.

Healthy control (CTRL): an anthropometrically-matched healthy male (27 yr, 74 kg, 178 cm) with no history of recent – general or musculoskeletal – health problems volunteered to be a control subject. An average of both legs' values, for all parameters, was used in this report to provide comparison to the ATR subject.

Achilles tendon pain (ATP): a unilateral (left) chronic Achilles tendon pain patient (26 yr, 72 kg, 181 cm) was also examined. The subject had tendon pain for 5 months without any other major health problems. His results were used to compare the effects of eccentric calf muscle training on glucose uptake patterns with the ATR subject. The symptomatic (PAIN) and asymptomatic (NOPAIN) legs were compared with OPER and UNOP legs of the ATR subject, respectively.

All subjects were recruited through public advertisements.

2.2. Procedures

Measurements were conducted at the University of Jyväskylä, Finland. All components of the study were carried out within a day for each patient both before and after the eccentric rehabilitation. Measurements for CTRL were done only once. All subjects provided informed written consent before the data collection. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of South-Western Finland.

2.2.1. Subject preparation

At least 8 h of fasting was required before the PET scans to ensure stable metabolic conditions between the subjects. Peripheral venous access catheters were placed into the antecubital veins of both arms: one for venous blood sampling and one for [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) tracer administration.

2.2.2. Plantarflexion motor task

Maximal voluntary isometric contraction (MVIC) force of ankle plantarflexors was measured three times, alternately with each leg while positioned in a dynamometer as described previously (Masood, Kalliokoski, Bojsen-Møller, et al., 2014). From the trial with the greatest force, a 30% target level was calculated and used during the submaximal plantarflexion tasks for individual leg. Familiarization with the equipment and the plantarflexion task was achieved by performing several unilateral submaximal contractions for each leg. Subsequently, subjects long-sat (ankle in neutral position; knee in full extension; hip in 90° flexion) in the exercise apparatus on the floor and performed the plantarflexion motor task (Masood, Bojsen-Møller, et al., 2014). The task comprised multiple sets of five unilateral submaximal, isometric voluntary contractions each at 30% MVIC for the respective leg. The duration of each contraction was 5 s followed by a 5-s rest period and the legs were alternated after every set. Subjects were provided with instantaneous visual feedback regarding both the target force level and their own motor attempt on a monitor screen. After two sets of warm-up contractions from each leg to reach steady-state milieu, ~150 MBq of [^{18}F]-FDG tracer was injected intravenously. This was followed by performance of 10 sets of the task from each leg. The total post-injection exercise time was about 15 min. Plasma sampling for blood radioactivity determination started simultaneously with the tracer injection and was repeated several times throughout the plantarflexion task and the subsequent PET scan (Masood, Kalliokoski, Magnusson, et al., 2014). Immediately following the plantarflexion task, the subjects were moved to the