Scand J Med Sci Sports 2012: 22: e55–e63
doi: 10.1111/j.1600-0838.2012.01475.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Metabolic activity in early tendon repair can be enhanced by intermittent pneumatic compression

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Accepted for publication 5 April 2012

Since Achilles tendon healing is protracted, more knowledge of metabolites known to meet the demands for biosynthesis and proliferation is needed. We hypothesized that essential metabolites, glutamate, glucose, lactate, pyruvate and glycerol, are present and upregulated in healing Achilles tendons. We moreover hypothesized that adjuvant intermittent pneumatic compression (IPC), which increases blood flow, upregulates metabolite concentrations. Twenty patients with acute Achilles tendon rupture were recruited, operated, and included. The control group, 15 patients, received plaster cast immobilization, while five patients received adjuvant foot IPC beneath the plaster cast. At 2 weeks postoperatively, microdialysis of the healing and contralateral intact Achilles tendons was followed by quantification of metabolites. Healing compared to intact tendons of the controls exhibited significantly increased concentrations (mM) of glutamate (60 ± 14 vs 20 ± 11), lactate (1.15 ± 0.60 vs 0.64 ± 0.35), and pyruvate (81 ± 29 vs 35 ± 25, μM). Healing tendons of the IPC vs control group displayed higher levels of glutamate (84 ± 15 vs 62 ± 16) and glucose (3.44 ± 0.62 vs 2.62 ± 0.72); ($P < 0.05$) and trends toward higher concentrations of pyruvate, lactate, and glycerol ($P < 0.10$). The present study demonstrates that early Achilles tendon repair entails and upregulates local essential metabolites. This metabolic response can, during tendon healing with plaster cast immobilization, be promoted by adjuvant IPC.

In Achilles tendon repair, the time until healing is protracted and still associated with a high degree of complications (Haggmark & Eriksson, 1979; Wong et al., 2002; Nilsson-Helander et al., 2010). This may partly be due to a sparse blood circulation and a low metabolic activity, which are even more restricted during limb immobilization (Boushel et al., 2000; Kjaer et al., 2000; Bring et al., 2010; Magnusson et al., 2010; Schizas et al., 2010a). One adjuvant treatment for improving peripheral circulation and hypothetically also enhancing tissue metabolism is intermittent pneumatic compression (IPC; Anglen et al., 1998). IPC was recently demonstrated to improve soft tissue repair and experimental Achilles tendon repair by increasing tissue proliferation including enhanced angiogenesis, nerve ingrowth, collagen formation, as well as increased tensile strength during immobilization (Dahl et al., 2007; Schizas et al., 2010a; Khanna et al., 2008). Vessel and nerve ingrowth are considered critical for the delivery of metabolites and neuronal transmitters, including glutamate, to the repair site (Ackermann et al., 2009).

*Both first authors contributed equally to the production of this manuscript.

Whether essential metabolites, glutamate, glucose, lactate, pyruvate, and glycerol are present in the human Achilles tendon, specifically during healing after rupture, is mostly unknown (Kjaer et al., 2000). Glutamate, however, has recently been identified in the healing tendon and is regarded to be involved in the repair process (Molloy et al., 2006; Ackermann et al., 2009). Glutamate is also involved in the carbohydrate metabolism together with the vital metabolites glucose, lactate, pyruvate, and glycerol (Im et al., 1976; Langberg et al., 1999; Kjaer et al., 2000). Each of these metabolites is needed for tissue repair and cell proliferation (Im et al., 1976; Langberg et al., 1999; Kjaer et al., 2000). Glucose provides the cells with energy, and lactate production at the tendon repair site has been demonstrated to enhance collagen synthesis (Klein et al., 2001). Both pyruvate and glycerol are basic structural elements in the energy metabolism involved in wound healing.

In the present study, we hypothesized that vital metabolite concentrations would be elevated during early human Achilles tendon repair, and that this metabolic activity could be stimulated by adjuvant IPC during the 2 weeks of plaster immobilization.

To answer this question, patients with acute Achilles tendon rupture were recruited, operated on, and received either conventional treatment with plaster cast immobilization or, for the intervention group, adjuvant foot IPC beneath the plaster cast. At 2 weeks postoperatively, microdialysis of the healing and contralateral intact Achilles tendons was followed by enzymatic quantification to assess metabolic activity, i.e., the concentrations of glutamate, glucose, lactate, pyruvate, and glycerol at the healing site.

Materials and methods

Patients

In this study, 20 patients with acute Achilles tendon rupture were between August 2010 and February 2012 recruited at the Karolinska University Hospital, Stockholm, Sweden. Patients with acute Achilles tendon ruptures, diagnosed by palpation and positive calf squeeze test, were operated on. Postoperatively, the first 10 patients were randomized in blocks of five into the two treatment groups, while the remaining 10 patients in the control group were recruited at a later time point. The control group, 15 patients, received conventional treatment with initially 2 weeks of plaster cast immobilization in 30 degrees of plantar flexion. The treatment group received adjuvant IPC beneath the plaster cast immobilization.

Patients between 16 and 75 years of age with an Achilles tendon rupture were included in the study if they were operated on within 72 h after injury. Exclusion criteria were diabetes mellitus, prior Achilles tendon rupture on the same limb, achillodynia, previous incidences of thromboembolism, and treatment with anticoagulants.

All participants received oral and written information about purpose and procedures of the study and provided written informed consent. Ethical approval was obtained from the Regional Ethical Review Board in Stockholm, Sweden.

Table 1. Patients characteristics of the intermittent pneumatic compression (IPC) group and the control group

Patient	Sex	Age	IPC usage*	IPC usage†	Smoker
IPC group					
1	M	39	45	66	0
2	M	47	47	55	0
3	M	43	146		0
4	M	49	77	98	0
5	M	39	84	60	0
Mean		**43.4**	**79.8**	**69.8**	0
SD		4.6	40.9	19.4	
1	M	42			0
2	M	49			0
3	M	33			1
4	F	34			0
5	M	46			0
6	M	31			0
7	M	33			1
8	M	41			0
9	M	40			0
10	M	27			0
11	M	30			0
12	M	45			0
13	M	39			0
14	M	33			0
15	M	51			0
Mean		**38.3**			0
SD		7.4			

*IPC usage as monitored by the device.

†IPC usage as assessed by the patient.

IPC, intermittent pneumatic compression

Intermittent pneumatic compression

IPC treatment was started within 3 h postsurgery and applied for 2 weeks. An inflatable cuff was placed under the arch of the foot of the subject, underneath the plaster cast. Cyclic inflation of the cuff induced pressure on the venous plexus of the foot, which produced increased venous backflow and increased arterial and interstitial circulation. Only the injured side was treated. The A-V Impulse™ foot compression system (Covidien, New Haven, CT, USA) was used and the settings were 130 mm Hg pressure, 1 s pressure duration, 20 s compression frequency. The subjects were instructed to use IPC for at least 6 h daily, and to monitor their IPC treatment by keeping a log book. IPC usage was also monitored by the device itself, see Table 1.

Microdialysis

To assess tendon healing, microdialysis followed by metabolite analysis were performed in principle as described by Langberg et al. (1999). Microdialysis was conducted at the 2-week postoperative control, when the plaster cast and the IPC device were removed. The subjects were instructed not to eat, smoke, or use snuff for at least 1 h before the appointment. Only one subject was a smoker, see Table 1. The subjects had the option of receiving analgesia in the form of codeine and paracetamol taken orally, in order not to interfere with the local tissue metabolism.

A microdialysis catheter (CMA 71; CMA Microdialysis AB, Solna, Sweden; 100 kDa molecular cutoff, 0.5 mm outer diameter; 30 mm in length) was introduced, under ultrasound guidance, from the lateral distal aspect of the heel into the peritendinous space 2–5 mm ventral to the Achilles tendon. The lateral approach was chosen in order to avoid the healing scar since most surgeons choose a slightly medial incision on the Achilles tendon. The active part of the membrane was placed as close to the rupture site as possible on the injured side and with approximately the same distance, 4 cm, to the calcaneal bone on the contralateral side.

After insertion of the catheters, the subject was lying prone on a gurney during the entire microdialysis investigation in order not to alter the position of or damage the catheter. A perfusion fluid (Macrodex®) was pumped (CMA 107; CMA Microdialysis, Solna, Sweden) through the inner tube of the catheter into the space between the inner tube and the semipermeable catheter membrane, where the exchange between the interstitial fluid and the perfusion took place. The fluid was transmitted from the catheter and was finally collected in a vial (Microvial, CMA Microanalysis AB, Solna, Sweden). The perfusion speed was set at 1.0 µL/min. The samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS Clinical Microdialysis Analyzer (CMA Microdialysis AB, Solna, Sweden). Because of the lingering effects of the insertion trauma and the possible differences in fluid pump adjustment during the first few minutes, the first of the four vials was not considered reliable and thus not included in the calculations. The treatment group had IPC applied bilaterally during the microdialysis examination to investigate the instantaneous effects of IPC as well.

Metabolite analysis

The substances analyzed were the metabolites lactate, glucose, pyruvate, and glycerol, and the neurotransmitter glutamate. The

ISCUS analyzer was calibrated before every analysis using a commercially available set of reagents (Reagent Set B, CMA Microdialysis AB, Solna, Sweden). The greatest advantage of this type of analysis is that it can be performed instantly, thus eliminating the risk of confounding factors, e.g., associated with degradation of metabolites during storing and freezing of the samples. No calculations of relative recovery were made because of reported unequal results using different methods of assessing recovery (Widegren et al., 2010). A prior study, however, with similar setup demonstrated a recovery of 48–62% (range) at rest and 70–76% during exercise for glycerol and glucose (Langberg et al., 1999).

Statistical methods

All variables were summarized with standard descriptive statistics such as mean, standard deviation, and frequency. Differences between the IPC and control group were analyzed with the non-parametric Mann–Whitney *U*-test, and differences between the injured and intact legs with Wilcoxon matched pairs test. The significance level in all analyses was 5% (two-tailed). A power analysis (a = 0.05, b = 0.8) on available data showed that five patients in each group would give significant results. The power was however low, and therefore, 10 extra controls were included. The statistical power allowed detection of only large effect sizes, i.e., 0.80 and higher. Thus, trends at the 10% level were also commented and denoted 'almost significant' to compensate for the high risk for type II errors. A *post hoc* power analysis (a = 0.05, b = 0.8) for the levels of pyruvate, which in the current study only demonstrated a trend toward significance between the IPC and control group, demonstrated a need for 10 patients in each group.

Results

Twenty patients were included from August 2010 to February 2012. The patient groups exhibited no significant differences in age, sex, or smoking habits – except a mean 70–80 h application of adjuvant IPC in the treatment group (Table 1).

Control group: Metabolites in the healing vs intact contralateral tendons (Table 2)

The healing Achilles tendons exhibited at 2 weeks postoperatively significantly higher levels of glutamate (59.8 ± 13.9 vs 19.9 ± 11.0 mM; $P = 0.003$), lactate (1.2 ± 0.6 vs 0.6 ± 0.4 mM; $P = 0.007$), and pyruvate (80.6 ± 29.1 vs 34.7 ± 25.1 μM; $P = 0.001$) compared to the contralateral intact tendons (Figs 1, 3, 4). No significant differences were found in levels of glucose ($P = 0.807$), glycerol ($P = 0.345$), or in the lactate/pyruvate ratio ($P = 0.307$; Figs 2, 5, 6).

IPC group: Metabolites in the healing vs intact contralateral tendons (Table 3)

Metabolite upregulations were observed in the healing Achilles tendons of the IPC-treated group as compared to the intact, contralateral tendons. Thus, significantly higher concentrations of glutamate (84.4 ± 14.7 vs 16.0 ± 9.1 mM; $P = 0.043$), glucose (3.4 ± 0.6 vs 2.5 ± 1.1 mM; $P = 0.043$), lactate (1.8 ± 0.6 vs 0.8 ± 0.3 mM; $P = 0.043$), and pyruvate (112.7 ± 33.0 vs 39.9 ± 19.4 μM; $P = 0.043$) were found (Figs 1–4). However, the glycerol levels ($P = 0.465$) and the lactate/pyruvate ratio ($P = 0.500$) did not display any significant changes (Figs 5, 6).

IPC vs control group: Metabolites in the healing tendons (Table 4)

The levels of glutamate (84.4 ± 14.7 vs 62.4 ± 16.0 mM; $P = 0.035$) and glucose (3.4 ± 0.6 vs 2.6 ± 0.7 mM; $P = 0.04$) were significantly higher in the IPC group as compared to the healing tendons of the control group (Figs 1, 2). There were also almost significant trends toward increases in the levels of pyruvate (112.7 ± 33.0 vs 80.6 ± 29.1 μM; $P = 0.089$), lactate (1.8 ± 0.6 vs 1.2 ± 0.6 mM; $P = 0.064$), and glycerol (83.3 ± 6.6 vs 77.6 ± 46.7 μM; $P = 0.057$; Figs 3–5) but no such trends regarding the lactate/pyruvate ratio ($P = 0.76$; Fig. 6).

IPC vs control group: Metabolites in the intact tendons (Table 5)

No significant differences were detected in the metabolite levels of the intact tendons that were IPC treated compared to the intact tendons of the control group (Figs 1–6).

Discussion

The present study demonstrates specific increases in metabolite concentrations during early human Achilles

Table 2. Metabolite levels in the healing and intact contralateral tendons of the control group

Control group	Healing tendons			Intact tendons			*P*	% Change
	n	M	SD	M	SD	*z*		
Glutamate (mM)	11	59.8	13.94	19.9	11.01	2.93	0.003	200
Pyruvate (μM)	15	80.6	29.10	34.7	25.14	3.41	0.001	132
Lactate (mM)	13	1.15	0.60	0.64	0.35	2.69	0.007	79
Glucose (mM)	14	2.60	0.75	2.56	0.56	0.25	0.807	2
Glycerol (μM)	13	82.5	48.14	86.3	26.81	0.94	0.345	–4
L/P × 1000	15	20.9	14.95	32.7	31.23	1.02	0.307	–36

SD, standard deviation.

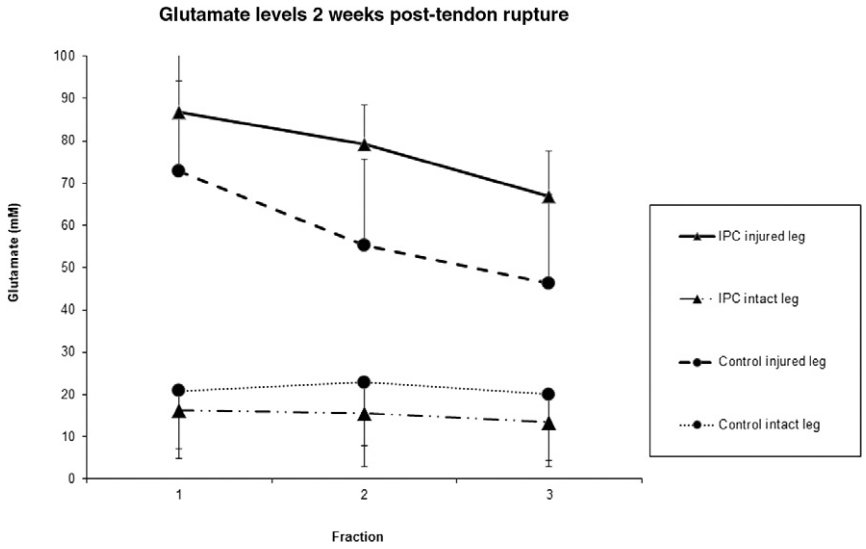

Fig. 1. Glutamate concentrations from microdialysis probes placed peritendinously ventral to the ruptured and contralateral intact Achilles tendon in six patients with adjuvant intermittent pneumatic compression and in five patients serving as controls. The perfusion speed was set at 1.0 μL/min and samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS analyzer. The first fraction was discarded and the three following fractions are presented as mean values ± STD. Glutamate was the metabolite exhibiting the highest increase in concentrations both during healing and after IPC treatment. There were significantly higher levels in the healing tendons of the IPC-treated group compared to the healing tendons of the control group.

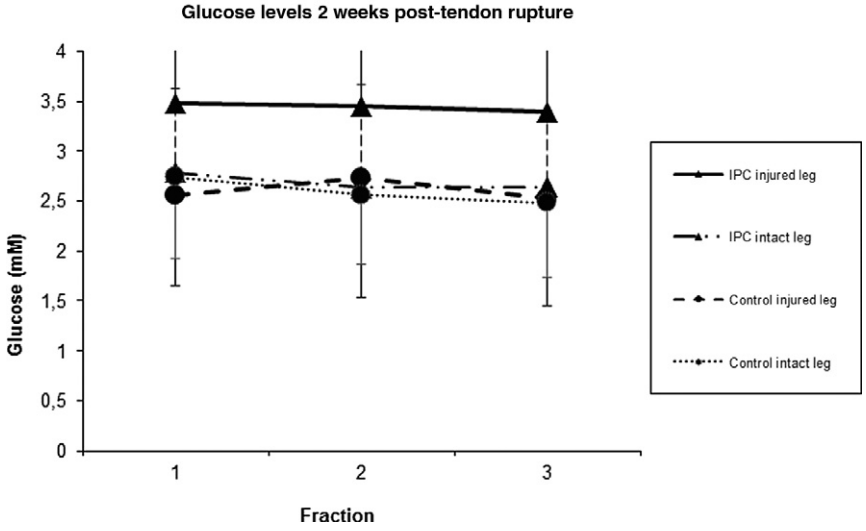

Fig. 2. Glucose concentrations from microdialysis probes placed peritendinously ventral to the ruptured and contralateral intact Achilles tendon in six patients with adjuvant intermittent pneumatic compression and in five patients serving as controls. The perfusion speed was set at 1.0 μL/min and samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS analyzer. The first fraction was discarded and the three following fractions are presented as mean values ± STD. The glucose levels displayed a significant increase in the healing tendons after IPC treatment as compared to the healing tendons of the control group.

tendon repair, which may be related to increased energy demands and a role in cellular proliferation. We furthermore provide evidence of elevated levels of the metabolites glutamate and glucose, implying activated amino acid and carbohydrate metabolic pathways, owing to adjuvant IPC.

At 2 weeks postsurgical repair of acute Achilles tendon ruptures, we demonstrated increased peritendinous levels of glutamate, lactate, and pyruvate in the healing tendons compared to the contralateral intact tendons. This indicates that the upregulated substances observed are related to activated local metabolic pathways involved in Achilles tendon repair. Interstitial metabolite concentrations in the peritendinous region have been demonstrated to correlate with corresponding concentrations within the Achilles tendon proper (Langberg et al., 2002).

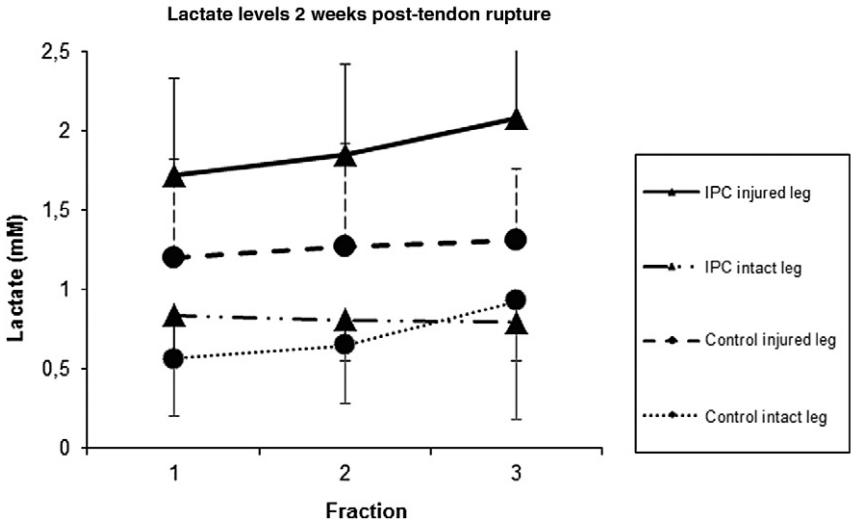

Fig. 3. Lactate concentrations from microdialysis probes placed peritendinously ventral to the ruptured and contralateral intact Achilles tendon in six patients with adjuvant intermittent pneumatic compression and in five patients serving as controls. The perfusion speed was set at 1.0 μL/min and samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS analyzer. The first fraction was discarded and the three following fractions are presented as mean values ± STD. Lactate levels increased during healing in both the IPC and control groups. There was a trend toward increased lactate levels in the healing tendons of the IPC-treated group compared to the healing tendons of the control group.

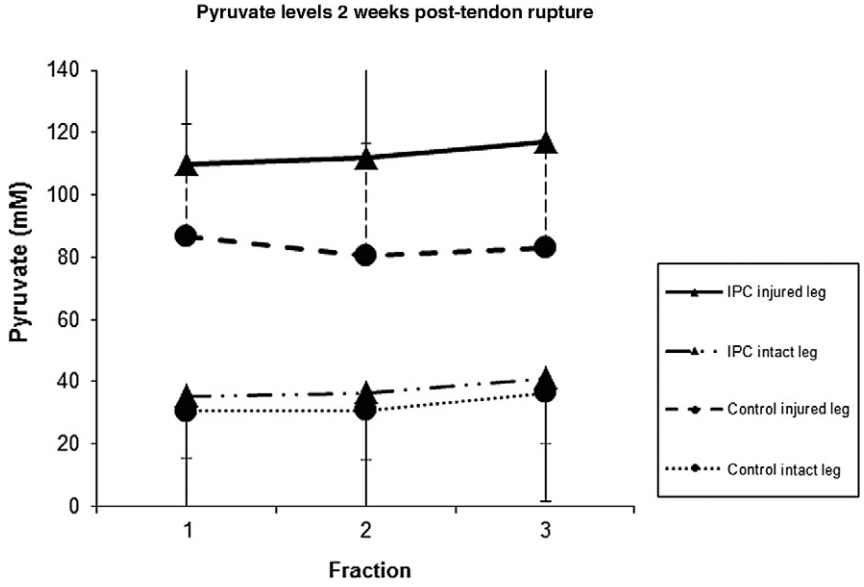

Fig. 4. Pyruvate concentrations from microdialysis probes placed peritendinously ventral to the ruptured and contralateral intact Achilles tendon in six patients with adjuvant intermittent pneumatic compression and in five patients serving as controls. The perfusion speed was set at 1.0 μL/min and samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS analyzer. The first fraction was discarded and the three following fractions are presented as mean values ± STD. Pyruvate concentration increased during healing in both the IPC and control groups. There was a trend toward increased pyruvate levels in the healing tendons of the IPC-treated group compared to the healing tendons of the control group.

The around twofold to fourfold elevations found in glutamate concentrations in the healing tendons of the control group are in agreement with a microarray study on rat Achilles tendon repair showing upregulated glutamate signaling during healing (Molloy et al., 2006). Thus, nerve ingrowth and subsequent release of several neuronal transmitters, including glutamate, have recently been identified in tendon healing and are considered to be involved in the repair process (Ackermann et al., 2009). Glutamate receptors have been identified on tendon cells, nerves, and blood vessels (Schizas et al., 2010b). Conceivably, glutamate may be involved in

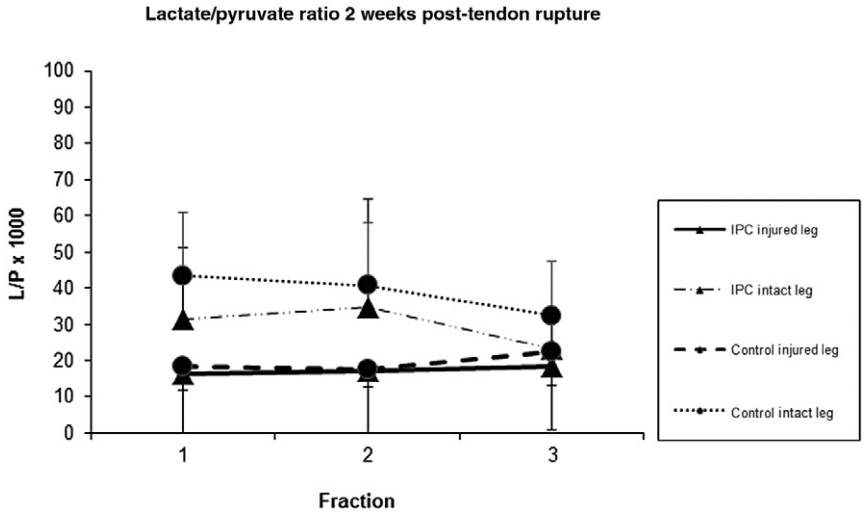

Fig. 5. The lactate/pyruvate ratio did not display any significant differences between the groups.

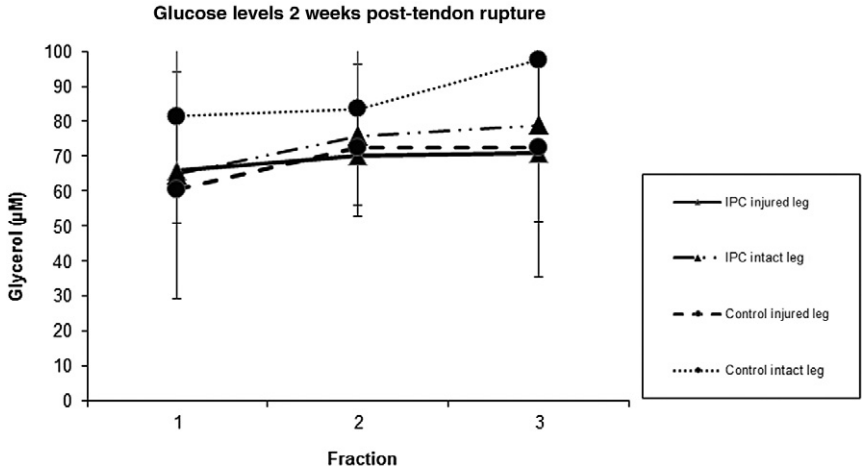

Fig. 6. Glycerol concentrations from microdialysis probes placed peritendinously ventral to the ruptured and contralateral intact Achilles tendon in six patients with adjuvant intermittent pneumatic compression and in five patients serving as controls. The perfusion speed was set at 1.0 µL/min and samples were collected every 30 min during 2 h and were instantly analyzed using an ISCUS analyzer. The first fraction was discarded and the three following fractions are presented as mean values ± STD. Glycerol was the metabolite that exhibited the least variation between the groups.

Table 3. Metabolite levels in the healing and intact contralateral tendons of the IPC group

IPC group	Healing tendons			Intact tendons			*P*	% Change
	n	M	SD	M	SD	*z*		
Glutamate (mM)	5	84.40	14.71	16.00	9.14	2.02	0.043	427.5
Pyruvate (µM)	5	112.70	33.04	39.89	19.40	2.02	0.043	182.7
Lactate (mM)	5	1.79	0.56	0.75	0.28	2.02	0.043	136.9
Glucose (mM)	5	3.44	0.62	2.51	1.14	2.02	0.043	37.2
Glycerol (µM)	4	83.30	6.60	70.77	32.13	0.73	0.465	17.7
L/P × 1000	5	16.40	4.46	25.20	14.09	0.67	0.500	–34.9

SD, standard deviation.

Table 4. Metabolite levels in the healing tendons comparing the IPC and control groups

Healing tendons	IPC group			Control group			*z*	*P*	% Change
	n	M	SD	*n*	M	SD			
Lactate (mM)	5	1.79	0.56	14	1.17	0.58	1.85	0.064	53
Pyruvate (μM)	5	112.7	33.04	15	80.6	29.10	1.70	0.089	40
Glutamate (mM)	5	84.4	14.71	12	62.4	16.00	2.11	0.035	35
Glucose (mM)	5	3.44	0.62	15	2.62	0.72	2.05	0.040	31
Glycerol (μM)	4	83.3	6.60	15	77.6	46.69	1.90	0.057	7
L/P × 1000	5	16.4	4.46	15	20.9	14.95	0.31	0.760	–22

IPC, intermittent pneumatic compression; SD, standard deviation.

Table 5. Metabolite levels in the intact tendons comparing the IPC and control groups

Intact tendons	IPC group*			Control group			*z*	*P*	% Change
	n	M	SD	*n*	M	SD			
Lactate (mM)	5	0.75	0.28	14	0.63	0.33	0.74	0.459	19
Pyruvate (μM)	5	39.9	19.40	15	34.7	25.14	0.74	0.458	15
Glucose (mM)	5	2.51	1.14	14	2.56	0.56	0.28	0.781	–2
Glycerol (μM)	4	70.8	32.13	13	86.3	26.81	1.02	0.308	–18
L/P × 1000	5	25.2	14.09	15	32.7	31.23	0.31	0.760	–23
Glutamate (mM)	5	16.0	9.14	14	22.4	15.90	0.74	0.459	–28

*The intact tendons received IPC treatment during microdialysis only. This was performed to assess if any direct effects of IPC treatment could be noted.
IPC, intermittent pneumatic compression; SD, standard deviation.

potentiating tissue repair processes involved in cellular proliferation. Interestingly, a 10-fold glutamate upregulation has been observed in tendinopathy, and consequently, it has been speculated that glutamate has a role in excessive cell proliferation as well (Alfredson et al., 2001; Schizas et al., 2010b).

The observed increase in lactate and pyruvate may be related to intensified anaerobic and aerobic metabolism, respectively, in the repairing tendon. However, the ratio between lactate and pyruvate was not altered, indicating no oxygen deficiency during tendon healing. Interestingly, local lactate production in wounds increases synthesis of collagen I and III by gene transcription and posttranslational hydroxylation (Klein et al., 2001). Pyruvate is known among other things to promote wound healing tissue by augmenting the antioxidant response and acting antifibrotically (Harvey et al., 2010). Although both aerobic and anaerobic metabolism increased, the glucose and glycerol levels were unchanged at 2 weeks of tendon repair. This finding does not preclude that these metabolites may exhibit alterations in earlier phases of tendon healing. Increased glycerol concentrations indicate cellular breakdown (Marklund et al., 1997). This suggests that at 2 weeks, no cellular distress was present.

Adjuvant IPC treatment during the first 2 weeks of tendon healing significantly elevated the levels of glutamate and glucose as compared to the control group. The increased glutamate concentration obtained may be related to enhanced nerve ingrowth and neurotransmitter release, as has been experimentally demonstrated with IPC, or/and improved cellular amino acid metabolism in the tendon (Schizas et al., 2010a). The upregulated glutamate levels may hypothetically stimulate proliferation of endothelial cells on blood vessels and of tenocytes in the tendon proper to promote angiogenesis and tendon repair (Molloy et al., 2006; Schizas et al., 2010b).

The elevated glucose levels after IPC may be related to an increased local blood flow. In fact, IPC is known to promote both venous and arterial circulation (Kakkos et al., 2008), as well as to improve angiogenesis during tendon healing (Dahl et al., 2007). The effect of IPC may be paralleled with that of plantar flexion exercise contracting calf muscles and compressing the vessels, which increased the Achilles peritendon blood flow from around 2 to 15 mL/100 mL/min (Boushel et al., 2000). Elevated local glucose is considered to meet the bioenergetic and biosynthetic demands associated with cell proliferation. The other metabolites, pyruvate, lactate, and glycerol, also exhibited trends toward upregulation after compression treatment, indicating increased metabolism.

In this study, we chose not to assess the relative recovery, i.e., percentage of substance yielded from the microdialysis, as compared to actual tissue concentration since our aim was to compare the metabolite levels between the groups. One study with a similar set up of peritendinous microdialysis demonstrated a recovery of 48–62%

(range) in healthy individuals at rest for glycerol and glucose (Langberg et al., 1999). However, the literature shows difficulties in assessing recovery since different techniques show various results (Widegren et al., 2010). Moreover, our data on the intact limbs that received IPC during 2 h of microdialysis demonstrated no increase in metabolite levels compared to intact limbs without treatment. This indicates that the instantaneous effects of IPC on blood flow did not increase the relative recovery of metabolites.

In conclusion, this study demonstrated elevated levels of glutamate, lactate, and pyruvate at 2 weeks postsurgery comparing healing and intact human Achilles tendons. Adjuvant IPC produced increased concentrations of glutamate and glucose during Achilles tendon repair, which may reflect an upregulation of the neurotransmitter/amino acid and carbohydrate metabolism. Whether and to what extent adjuvant compression therapy is beneficial for tendon repair should, based on these data, be further investigated by clinical evaluations.

Perspectives

Achilles tendon repair is a protracted process, hampered by additional immobilization (Haggmark & Eriksson, 1979; Wong et al., 2002; Bring et al., 2010; Nilsson-Helander et al., 2010). Healing can be promoted by early mobilization and stimulated blood flow (Boushel et al., 2000; Kjaer et al., 2000; Bring et al., 2010; Magnusson et al., 2010; Schizas et al., 2010a). Little, however, is known about metabolic activity during tendon healing and if it can be enhanced (Boushel et al., 2000). The metabolite and neurotransmitter glutamate, assumed to play a role in tissue proliferation, is present in ingrowing nerves and vessels during Achilles tendon repair (Molloy et al., 2006; Ackermann et al., 2009). In experimental Achilles tendon rupture in rats, IPC was demonstrated to promote repair during immobilization (Schizas et al., 2010a) by enhancing nerve-vessel ingrowth and release of neuronal substances (Dahl et al., 2007).

The present study corroborates and translates the finding from animal studies of elevated presence of the metabolite/neurotransmitter glutamate in early repair by demonstrating a threefold upregulation at 2 weeks postsurgery of acute human Achilles tendon rupture. Moreover, adjuvant compression treatment during postoperative plaster immobilization has the ability to additionally elevate the concentration of glutamate at the repair site. The data from this study also show that during the healing process, essential metabolites can be assessed using microdialysis at the repair site. Metabolite levels should, in future studies, be linked to standardized assessments of tendon repair.

Key words: achilles tendon, healing, microdialysis, glutamate, glucose, lactate, pyruvate, glycerol.

Acknowledgements

This study was supported by the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet (project nr. SLL20100168), the American Orthopaedic Society for Sports Medicine, and the Swedish National Centre for Sports Research.

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