The effect of dynamic knee-extension exercise on patellar tendon and quadriceps femoris muscle glucose uptake in humans studied by positron emission tomography

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Kallioksi, Kari K., Henning Langberg, Ann Kathrine Ryberg, Celena Scheede-Bergdahl, Simon Doessing, Andreas Kjaer, Robert Boushel, and Michael Kjaer. The effect of dynamic knee-extension exercise on patellar tendon and quadriceps femoris muscle glucose uptake in humans studied by positron emission tomography. J Appl Physiol 99: 1189–1192, 2005. First published May 5, 2005; doi:10.1152/japplphysiol.00283.2005.—Both tendon and peritendinous tissue shows evidence of metabolic activity, but the effect of acute exercise on substrate turnover is unknown. We therefore examined the influence of acute exercise on glucose uptake in the patellar and quadriceps tendons during dynamic exercise in humans. Glucose uptake was measured in five healthy men in the patellar and quadriceps tendons and the quadriceps femoris muscle at rest and during dynamic knee-extension exercise (25 W) using positron emission tomography and [18F]-2-fluoro-2-deoxy-D-glucose ([18F]FDG). Glucose uptake index was calculated by dividing the tissue activity with blood activity of [18F]FDG. Exercise increased glucose uptake index by 77% in the patellar tendon (from 0.30 ± 0.09 to 0.51 ± 0.16, P = 0.03), by 106% in the quadriceps tendon (from 0.37 ± 0.15 to 0.75 ± 0.36, P = 0.02), and by 15-fold in the quadriceps femoris muscle (from 0.31 ± 0.11 to 4.5 ± 1.7, P = 0.005). The exercise-induced increase in the glucose uptake in neither tendon correlated with the increase in glucose uptake in the quadriceps muscle (r = −0.10, P = 0.87 for the patellar tendon and r = −0.30, P = 0.62 for the quadriceps tendon). These results show that tendon glucose uptake is increased during exercise. However, the increase in tendon glucose uptake is less pronounced than in muscle and the increases are uncorrelated. Thus tendon glucose uptake is likely to be regulated by mechanisms independently of those regulating skeletal muscle glucose uptake.

metabolism; connective tissue; imaging

TENDON TISSUE plays a central role in force transmission from skeletal muscles to bones and is subject to a considerable amount of overuse injuries associated with occupation and leisure exercise. The circulatory and metabolic adjustments that occur not only in the active skeletal muscle but also in the tendon may play a role in these pathophysiological changes. It has been demonstrated with the use of 133Xenon washout technique (11) and near-infrared spectroscopy (3) that blood flow increases in the tendinous and peritendinous region of humans during exercise. In addition, oxygen consumption is increased in the tendinous region (3), which is in good agreement with the presence of both oxidative and glycolytic enzymes in the connective tissues of the tendon (5, 7).

Whether the connective tissue of the tendon takes up energy substrates from the blood and, if so, how exercise affects nutritive uptake, are interesting questions in regards to an understanding of connective tissue physiology. Favoring the uptake during exercise, a recent positron emission tomography (PET) study showed the presence of glucose uptake in the Achilles tendon during exercise (4). However, because no resting measurements were performed in that study, it is currently not known to what extent glucose uptake increases from resting level during exercise-induced tendon strain. It was previously shown with the use of microdialysis that the glucose uptake was not changed in the peritendinous region during 30 min of intermittent isometric exercise at the workload of normal walking (11). However, as the load during that exercise type was rather moderate, and, furthermore, the method to measure glucose uptake might have been too imprecise to detect very small changes that may exist between the vascular and tissue compartments, it cannot be excluded that exercise does increase glucose uptake in the connective tissue.

In the present study we sought to load the patellar tendon with the use of one-legged dynamic knee-extension exercise (1) to compare glucose uptake simultaneously in the resting and exercising tendon and relate this to measures obtained in the quadriceps femoris muscle. Glucose uptake in the tendon and muscle was measured using PET and [18F]-2-fluoro-2-deoxy-D-glucose ([18F]FDG).

METHODS

Subjects. Five healthy men participated in this study (age 25 ± 5 yr, height 182 ± 7 cm/kg, weight 77 ± 8 kg/m2, and body mass index 23 ± 3). Written informed consent was obtained after the purpose, nature, and potential risks were explained to the subjects. The study protocol was reviewed and approved by the Ethical Committee of Copenhagen and Frederiksberg communities (11–140/03), and the study was performed in accordance with the Declaration of Helsinki.

Study protocol. This study on tendon glucose uptake was a part of a larger study primarily investigating skeletal muscle turnover, and microdialysis catheters were therefore inserted into the vastus lateralis muscle in the beginning of the study day. The fibers did not, however, interfere with the region that was used for determination of glucose uptake in muscle, and, furthermore, the fibers were neither sensed nor detected very small changes that may exist between the vascular and tissue compartments, it cannot be excluded that exercise does increase glucose uptake in the connective tissue.

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limiting for the exercise performance by the subjects. After this, the subjects were allowed to rest for 3 h during which two intravenous catheters were put into the antecubital veins in both arms. Thereafter, the subjects were moved to the knee-extension machine and one-legged exercise with the intensity of 25 W was started. Ten minutes after the beginning of the exercise 396 ± 27 MBq of [18F]FDG in 5 ml of saline was infused and blood sampling was commenced and continued until the end of the study. In total, 23 venous blood samples for the determination of blood radioactivity were taken. After the injection of the tracer the subject continued kicking for another 25 min. Immediately after the exercise, subjects were moved into the PET scanner and the PET scanning was performed as follows.

PET image acquisition and processing. For PET scanning, a GE Advance scanner (General Electric Medical Systems, Milwaukee, WI) was used. The scanner has 18 crystal rings forming 35 two-dimensional imaging planes spaced by 4.25 mm. In the emission scans, both legs distal to the midthigh were scanned in 3 × 4-min time frames from four different areas of the legs. After the emission scans, transmission scans for attenuation correction were performed for the four different areas of the leg using germanium-68 pin sources. The data sets were reconstructed using the filtered back-projection method with a Hanning filter. All data sets were corrected for dead-time and random coincidences. The axial and in-plane resolution of the reconstructed images was ~5 mm full width at half maximum.

Regions of interest. As the whole leg below the upper part of the thigh was scanned, the whole patellar tendon was within the imaging area and clearly visible in PET images. We analyzed the knee extensor tendon both 0–3 cm above (quadriceps tendon) and below (patellar tendon) the patella. In addition, one big region of interest covering the cross-section of the whole quadriceps femoris muscle was drawn on one mid-thigh plane.

Calculation of glucose uptake index. Glucose uptake index in the tendon and muscle was calculated by dividing the tissue radioactivity with blood radioactivity (16). Yokoyama and colleagues (16) recently compared this method to traditional graphical analysis (14) with an excellent linear relationship between absolute glucose uptake from graphical analysis and glucose uptake index from the simplified method (r = 0.968–0.984). The first time frames of the scanning (the first 4 min from the thigh area and the second 4 min from the knee area) were used for the analysis as also the blood sample from the respective time point. Because the PET imaging was performed immediately after exercise, the results reflect very well the uptake of [18F]FDG during the exercise period (6). Because the tracer content in the blood is very low (<5% of the injected amount left) 25 min after the tracer injection and exercise, the period between the end of exercise and the start of the scan has only a minor influence on the measured values of tendon or skeletal muscle glucose uptake.

Statistical analysis. Statistical analysis was performed with the SAS statistical program package version 8.2 (SAS Institute, Cary, NC). Student’s t-test was used for the comparison between the resting and exercising values and between the tendon and muscle values. The linear relationship between the variables was calculated using Pearson’s correlation coefficient. The P value <0.05 was considered statistically significant. The results are expressed as means ± SD.

RESULTS

Figure 1 shows representative PET images from the regions of patellar tendon, quadriceps tendon, and quadriceps muscle. Glucose uptake index was at the same level in both tendons and muscle at rest (Fig. 2). Exercise increased glucose uptake index by 77% in the patellar tendon, by 106% in the quadriceps tendon, and by 15-fold in the quadriceps femoris muscle (Fig. 2). Glucose uptake in the quadriceps tendon tended to be higher than in the patellar tendon during exercise (P = 0.07). The exercise-induced increase in the glucose uptake in neither tendon correlated with the increase in glucose uptake in the quadriceps muscle (r = −0.10, P = 0.87 for the patellar tendon and r = −0.30, P = 0.62 for the quadriceps tendon).

DISCUSSION

The findings in the present study show that glucose uptake into the human patellar tendon as to the quadriceps tendon is significantly increased during exercise (Fig. 2), although not to the extent seen in the skeletal muscle. Furthermore, glucose uptake seems to be enhanced more in the quadriceps tendon compared with the patella tendon in response to knee-extension exercise. Finally, the increase in tendon glucose uptake is not coupled to the increases in the adjacent skeletal muscle, indicating that regulation of glucose uptake in tendon represents a separate regulatory system and is not simply a secondary phenomenon to skeletal muscle.

These findings emphasize that tendon is a metabolically active tissue and that its energy demand is increased during
exercise in humans. It is well documented that blood flow increases in the peritendinous tissue during exercise in humans (3, 9, 11). Furthermore, it has been shown that there are oxidative enzymes within fibroblast and tenocytes of tendon (5, 7) and that the tendon oxygen consumption also increases during exercise (3). In addition to this it has been shown that a coupling exists between the exercise-induced drop in tissue oxygenation and increase in blood flow (3). Thus tendon is not simply a rigid tissue component mediating the forces generated by muscles into locomotion but can be stated to be a metabolically active tissue that most likely possess its own regulatory pathways to control blood flow in a manner that matches oxygen demand.

In a recent PET study (4), a significant glucose uptake in the Achilles tendon was observed during cycling exercise. However, the glucose uptake did not increase with the increasing exercise intensity in that study. This is most probably explained by only minor changes in the strain of the Achilles tendon with the increasing cycling intensity (4). The aforementioned study lacked the resting measurements and therefore it is not possible to estimate how pronounced the increase in tendon glucose uptake could have been from rest to exercise. In the present study the increase in glucose uptake was 77% in the patella tendon below the knee and 106% in the quadriceps tendon above the knee with one-legged dynamic knee-extension exercise at a moderate (1) workload of 25 W. As it can be calculated that knee extension provided a somewhat higher load on the quadriceps tendon than on the patellar tendon, it might be logical that the glucose uptake is larger in the quadriceps than in the patella tendon (Fig. 2). However, the present study does not allow for any conclusions regarding workload-related increase in tendon glucose uptake but only can state that it rises with exercise. Thus one of the future research focuses should be to study whether glucose uptake increases with the increasing exercise intensity and strain to tendon.

In a previous microdialysis study no significant increase in Achilles tendon glucose uptake was found with the plantar flexion exercise at the intensity comparable to normal walking (11). The reasons for these discrepancies between the studies may be related to the methodology used to measure glucose uptake. It is possible that in using the microdialysis technique small changes in glucose turnover may remain undetected (12). Noteworthy is also that in the study by Langberg et al. (11) glucose uptake was not measured in the tendon itself but in the peritendinous region. Although the results from a pig study suggest that the glucose concentration in the peritendinous tissue reflects the glucose concentration within the tendon (10), there may be differences in glucose uptake in these compartments.

The present study does not allow for any mechanistic explanation for the increased glucose uptake, but it is interesting that the magnitude of increase in glucose uptake in the tendon is not correlated to the rise in glucose uptake of the muscle. This suggests that the regulation of glucose uptake in tendon represents a separate regulatory system rather than being a passive secondary phenomenon to adjustment of glucose uptake in skeletal muscle. It cannot be stated whether the increased glucose uptake in tendon is primarily due to increased flow or is dependent on a higher active glucose transport and thus extraction. In accordance with the idea that blood flow regulation influences glucose uptake, it has been shown that vasodilatory substances like prostaglandins play a more dominating role in flow regulation during exercise of tendon than of skeletal muscle (2, 8, 15). The role of other potential vasodilators in the regulation of tendon blood flow and metabolism are poorly known and should be investigated in the future.

Studying tendon physiology using PET presents some methodological challenges. The diameter of the patellar tendon is around 8–20 mm and is therefore only a little greater than the resolution of PET scanners. In the previous PET study (4) a reasonable old ECAT 931 scanner with the resolution of 8 mm was used for the measurements, whereas the newer GE Advance with a resolution of 5 mm was used in the present study. This facilitated advanced precision in detection of differences in glucose uptake between the resting and exercising tendon. Another technical point that should be noted is the partial volume effect (13). That is, when the size of the measured object is small compared with the resolution of the scanner the true values may be underestimated depending on the activity of the tissue surrounding it (13). The region around the patellar tendon below the knee contains only connective tissues and bone with somewhat lower activity than in the tendon, and therefore, the values are not in any case increased by the partial volume effect. What is even more important, the activity in the surrounding area was not influenced by exercise, meaning that the observed increase in the tendon glucose uptake reflects the real change within the tendon. In the present study, glucose uptake was estimated using the ratio between tissue and blood activity (glucose uptake index). It has been shown that this index is almost perfectly linearly related to the quantitative activity (glucose uptake index). It has been shown that this index is almost perfectly linearly related to the quantitative glucose uptake values obtained using graphical analysis that is the golden standard for analyzing glucose uptake from [18F]FDG-PET images. Thus, although it is semiquantitative in nature, the glucose uptake index reflects linearly the absolute changes in tissue glucose uptake.

In summary, the present study shows that exercise increases quadriceps and patellar tendon glucose uptake. These findings emphasize that tendon is a metabolically active tissue and that its substrate uptake is increased during exercise and that this is regulated independently of skeletal muscle glucose uptake during exercise.

Fig. 2. Muscle glucose uptake index in the resting (open bars) and exercising (black bars) patellar and quadriceps tendons and quadriceps femoris muscle. *P < 0.05 and **P < 0.01 compared with respective resting value. ††P < 0.01 compared with tendon exercise values.
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