Slow training effect on intracellular lipid in skeletal muscle

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Target Audience This information will be beneficial for endocrinologist, sports trainer, and patient with lifestyle related disease.

Purpose

There is much interest in exercise training in the context of chronic disease and ageing, as well as in sports. Broadly, aerobic training has favourable effects on cardiovascular function and oxidative metabolism (1, 2) while resistance training improves muscle mass and strength (3-5). In the clinical context high-intensity resistance exercise may produce undesirable increases in blood pressure, and this has prompted investigation of low-intensity resistance exercise with slow movement and tonic force generation (6). This 'slow training' (7) has been shown to be effective at increasing cross-sectional area and isometric strength, probably by inducing muscle deoxygenation (6), which may also partly explain beneficial effects on vascular endothelial function (7).

There are complicated relationships between training state, aerobic function, insulin sensitivity and muscle lipid metabolism, on which the use of proton magnetic resonance spectroscopy (1H MRS) to measure intramyocellular lipid (IMCL) has in recent years thrown some light. High IMCL is an accompaniment of insulin resistance, and it is argued, causally linked to impaired insulin signalling via impaired fatty acid oxidation (8); at the other extreme of fitness, high IMCL is characteristic of aerobically-trained muscle (9) - a substrate-store accumulation analogous, it can be argued, to the accumulation of glycogen in resistance-trained muscle. We were interested in whether slow training would (via its effects on muscle oxygenation, vascular function or hypertrophy) have any local effect on IMCL. We set out to study this in healthy volunteers using a simple form of calf muscle exercise training, not requiring any special equipment. The purpose of this study was to evaluate slow training effects on focal fat metabolism in healthy normal male skeletal muscle with 1H MRS at 3T.

Methods

Twenty-three young healthy male volunteers aged 23-36 years were divided randomly into an exercise group (n=11) and a control group (n=12). Written informed consent was obtained from all volunteers, and the study had Ethical Committee approval from the University of Tsukuba, where the work was carried out. In the exercise group, all volunteers performed "calf raise" training of their dominant calf (i.e. the calf on the side of the dominant foot) regularly for 3 months, while volunteers in the control group performed no special physical training. All 23 dominant calves were studied by 1H MRS and MRI before the start of the study (baseline, 0M) then every month (1M, 2M, and 3M), the final assessment being performed 3 months after the start of training. All volunteers were asked to refrain from exercising for 48 hours before each scan. Calf muscle exercise training was carried out as follows. Standing on their dominant leg, braced with their arms against a wall, volunteers repeatedly raised themselves on their toes by plantar flexion, in a timed cycle in which slow raising and lowering each took 3 seconds; one set of 10 raising/lowering cycles therefore took 1 min, and volunteers did 3 sets each with 1 min rest in between. This was performed twice a week for 3 months.

1H MRS was performed in the supine feet-first position in a 3T clinical MR machine (Achieva, Novadual, Philips, Best, Netherlands). IMCL and EMCL in the soleus (SOL) muscle of the dominant calf were measured in both groups. The volume of interest (VOI) was determined at the slice showing the largest area of SOL. Measurements were performed at the same site and always at the same fixed position in every scan for each volunteer, assessed with reference to the baseline (0M) MRI scan. 1H MRS measurements were performed with a TORSO array coil, which has six QD-surface coils. The VOI size was 12 mm x 12 mm x 35 mm. A single voxel-localized 1H MRS acquisition was performed using a point-resolved spectroscopy (PRESS) sequence, both with and without water suppression, accomplished using three preceding chemical-shift–selective (CHESS) pulses (bandwidth, 140 Hz). Before spectroscopic acquisition, field homogeneity was optimized over the selected VOI by automatic shimming on tissue water. The following PRESS parameters were used: TR = 3000 ms; TE = 40 ms; number of points sampled = 1024; spectral width = 2,000 Hz; number of signal acquisition was 96 for metabolites 16 for water. Scan time was 5 min 24 s for data acquisition, before which shimming took about 5 min. Fitting of 1H MRS data was performed using LCModel (LA Systems). Data for IMCL (1.3 ppm) and EMCL (1.5 ppm) methylene protons were used for quantification. IMCL and EMCL estimates were automatically scaled to unsuppressed water peak. Conversion of concentrations into mmol per kg wet weight (WW) was performed using a recently described algorithm (10). Concentrations of EMCL CH2 and IMCL CH2 were computed as mmol per liter of muscle after correction for T1 and T2 relaxation effects of the unsuppressed water peak using LCModel's control parameter ATTH2O according to the following formula: exp(-TE/T2) [1-exp(-TR/T1)] (11) employing T1 and T2 values of water at 3.0 T (12). This value was divided by 31 assuming an average of 62 methylene protons per triglyceride, equivalent to 31 CH2 groups (10), and then by a tissue density of 1.05 kg/L to convert to mmol per kg wet weight (10).

The maximal cross-sectional area of the 23 calves for both groups was measured using anatomical T1-FFE to assess muscle hypertrophy. All cross-sectional areas of each scanned leg were traced on the screen to determine the thickest portion for each volunteer. Maximal cross-sectional area was compared between 0M and 3M in each group using a paired t-test. Isometric and isokinetic (30 degrees/sec) muscle strength of the dorsal side of the calf also measured with the Biodex system 4 (Biodex) machine at 0M and 3M in both groups. The change in muscle strength between 0M and 3M was also analyzed in each group using a paired t-test.

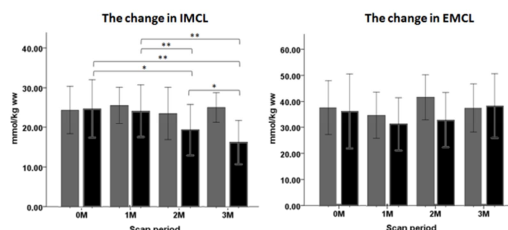
IMCL and EMCL obtained in each of the 23 SOL muscles in both groups were averaged for each period (0M, 1M, 2M, and 3M). Average IMCL and EMCL values were compared with two-factor ("group" and "scan period") ANOVA with repeated measures in each group.

Results & Discussion

The average maximum calf area in the exercise group was 4224 mm2 at 0M and 4379 mm2 at 3M; this slight increase was not statistically significant. Calf areas in the control group were almost identical (4338 mm2 and 4334 mm2, respectively) at 0M and 3M. Muscle strength showed statistically significant ((**P<0.01) increases in both isometric and isokinetic tests between 0M and 3M in the exercise group, but not in controls (Table 1).The time-course of IMCL and EMCL of the 12 SOL muscles in the control group and the 11 in the exercise group are shown in Figures. While IMCL did not change until 1M, it decreased gradually thereafter in the exercise group, where statistically significant differences were observed between 0M and 2M (*0.01<P<0.05), 0M and 3M (P<0.01), 1M and 2M (P<0.01), 1M and 3M (P<0.01), and 2M and 3M (0.01<P<0.05) by repeated measures with the Bonferroni post hoc test. No significant changes were observed for EMCL. The control group showed no significant changes for either lipid.

Table 1 Training effects on isometric and isokinetic muscle strength

Pre		Post	
A	B	A	B
Isometric			
71 (24)	78 (16)	136 (22)**	81 (18)
Isokinetic			
88 (25)	84 (20)	149 (25)**	89 (31)



Intramyocellular lipid (IMCL) is related to the pathogenesis of various lifestyle-related diseases, including diabetes mellitus (DM) (13, 14), and may have a causal role in insulin resistance (15, 16). It has been widely reported that exercise therapy can reduce IMCL, resulting in the improvement of insulin resistance in patients with lifestyle-related diseases (17-19). The slow training method used in this study does not induce skeletal muscle hypertrophy: however, it appears to be able to reduce local IMCL content in healthy volunteers. It may therefore be that slow training has potential for application in lifestyle-related diseases. The mechanism of the effect is not clear. Calf raise training delivers prolonged stress to the muscle of the calf. The SOL muscle has the highest proportion of slow-twitch fibers among calf muscles (20), and may therefore be most susceptible to improvements in mitochondrial β-oxidation of fatty acids, resulting in a gradual decrease in IMCL.The effect on IMCL was not entirely consistent across individuals: two participants showed slight increase or no change, and the size of the decrease in IMCL was variable between participants. We did not consider any change of weight, and did not control food intake during the experiment period. As there is a correlation between IMCL and weight, body mass index, and the amount of visceral fat (8, 21), this may contribute to variability between volunteers.

Conclusion

Long-term slow training, which is a simple and well-tolerated form of exercise, can reduce local IMCL content in healthy volunteers. Although the mechanism underlying IMCL decrease associated with slow training is not known, it may be that slow training has potential as a treatment strategy for patients with lifestyle-related diseases, given the known relation between IMCL and insulin resistance.

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