

The effects of statins on ³¹P MRS measured skeletal muscle metabolite content and function

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Introduction:

Statins (HMG-CoA reductase inhibitors) are commonly used to lower cholesterol as well as reduce risk and rate of vascular disease (O'Conner et al., 2004, Ridker et al., 2009). Consequently, this has led to more aggressive and widespread statin therapy (Koren and Hunninghake 2005, Wiviott et al., 2005). Inhibitors of HMG-CoA reductase block an early step in the cholesterol biosynthetic pathway resulting in the inhibition of mevalonate production which probably contributes to the vast pleiotropic effects. However, preventing mevalonate production interferes with important processes linked to muscle membrane stability, cytoskeleton structure, muscle function and muscle repair (Baker 2006). The purpose of this study was to determine if short-term high dose statin therapy affects resting skeletal muscle metabolites and skeletal muscle aerobic capacity using magnetic resonance spectroscopy.

Methods:

Thirteen adults (6 females, 45±9 yrs old, BMI=27±3, mean±SD) were tested before and after 4 weeks of 80mg atorvastatin calcium after providing written informed consent. ³¹P MRS (GE 3T Signa® HDx MR scanner) was used to acquire spectra from the quadriceps muscle at rest, during exercise and during recovery after exercise (Figure 1). Spectra were acquired (51.7 MHz, 2500 Hz sweep width, 1024 complex points, 3s TR, 60° pulse) with a circular 12 or 15 cm diameter linear transmit-receive surface coil. Three 90-s cycles of dynamic knee exercise (2 contractions per 3 s) followed by 300-s recovery were averaged and PCr resynthesis was measured using a mono-exponential model to estimate the time constant (tau, τ) of PCr recovery. Twenty resting spectra were averaged for resting levels of ³¹P metabolites. Free induction decays were processed and spectra were quantified with in-house software (Winspsa) using a lorentzian fit (for measures of PCr, Pi and pH) and simple sum (for PDE and ATP). pH was calculated from the chemical shift of Pi relative to PCr (Harkema et al., 1997). Paired t-tests were used to evaluate changes in serum cholesterol, muscle metabolites, PCr resynthesis rate and exercise parameters.

Results:

Following 4 weeks of 80-mg atorvastatin, total cholesterol decreased from 218±48 to 126±22 mg/dL (p<0.05, mean±SD). There were no differences in resting metabolites following short-term statin use (Table 1). PCr resynthesis was ~11% slower following statin therapy (Table 1, Figure 2, p<0.05). Minimum pH following exercise and force during exercise was not different pre- vs. post-statin (Table 1, p>0.05).

(n=13)	Pre-statin	Post-statin
PCr/Pi	9.16 ±0.40	10.07± 0.40
τ PCr resynthesis rate (s)*	44.7±2.9 s	49.5±3.6 s
pH rest	7.009±0.007	6.998±0.006
pH minimum	6.977±0.015	6.948±0.070
PDE/γATP	0.394±0.042	0.374±0.036
Exercise force (kg)	16.7±1.8	16.5 ±1.6

Table 1. ³¹P metabolites and exercise data, mean ± SE

*p<0.05, Pre vs. Post

Discussion:

High dose atorvastatin treatment did not change resting skeletal muscle metabolites following short-term use. In particular, statins did not increase PDE, a marker of cell membrane turnover, although previous data showed greater muscle PDE in skeletal muscle of statin users (Slade et al. 2006). Statins could plausibly alter coenzyme Q production, an important component of the electron transport chain involved in aerobic ATP production (see Baker 2006). Interestingly, statins prolonged PCr resynthesis after short-term high dose treatment in middle-aged adults. These results suggest that statins alter skeletal muscle function as reflected by changes in aerobic metabolism.

References:

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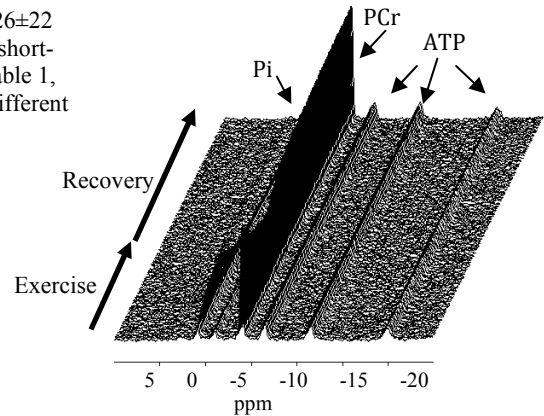


Figure 1. ³¹P spectra acquired during exercise and recovery from a representative subject. Spectra are an average of three gated cycles.

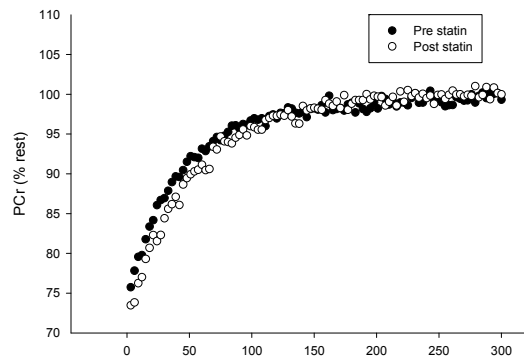


Figure 2. Group mean PCr resynthesis following dynamic exercise before (Pre) and after (Post) statin therapy.

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