Elevated muscle phosphodiesters in ^{31}P-NMR spectra of subjects on statins.

R. A. Meyer[1], J. M. Slade[1], T. F. Towse[1], M. C. DeLano[2]

[1]Physiology, Michigan State University, East Lansing, Michigan, United States, [2]Radiology, Michigan State University, East Lansing, Michigan, United States

INTRODUCTION

Cholesterol lowering drugs, namely statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely prescribed to control blood cholesterol and lipoprotein levels. Furthermore, the beneficial effects of statins may extend to treatment of conditions not obviously related to hyperlipidemias, such as osteoporosis and Altzheimer's disease (1). Thus, statin use in the aging population is likely to increase. Unfortunately, in some patients statins cause muscle pain and weakness, and more rarely, statins can cause serious myopathy and rhabdomyolysis (2). Previous studies showed that muscle phosphodiesters (PDE, primarily glycerophosphocholine) are elevated in individuals with fibromyalgia (3) or muscular dystrophy (4), suggesting that elevation of PDE might provide a non-specific index of myopathy. Therefore, the purpose of this study was to compare ^{31}P-MRS measured PDE content in statin users vs. age-matched control subjects.

METHODS

Ten statin users (4 female, age 48±11 [SD] yrs.) and ten control subjects with no history of statin use (5 females, age 48±7 yrs) were recruited from the University community. The project was approved by the University IRB, and subjects gave informed, written consent. The statin group was heterogeneous with respect to drug (7 atorvastatin , 2 pravastatin, 1 rosuvastatin), dosage (10-40mg/day) and duration of treatment (0.1-10 years), and none reported chronic muscle pain or weakness. ^{31}P-NMR spectra (51.7MHz, 2500 Hz sweep, 1K points, 60 NEX, TR 3s) were acquired on a 3T GE Horizon system via an 8x5 cm elliptical surface coil placed over the belly of the tibialis anterior muscle. A fast T1-weighted localizer image was acquired in order to confirm the location of the coil, visualized from a small water vial mounted in its center (FIG 1). Spectra were filtered with a 10-15 Hz exponential before FFT, and peak areas were manually integrated by a blinded observer. Muscle pH was calculated from the chemical shift of the Pi peak.

RESULTS

Illustrative spectra from a control and statin subject appear in Figs. 2 and 3, respectively. The PDE/γ ATP ratio was on average 57% greater in statin users (p=0.041, 2-tailed t-test) compared to controls, while PCr/ATP PCr/Pi, and pH were similar in the two groups (Table).

	CONTROL		STATIN	
	Mean±SE	Range	Mean±SE	Range
PDE/γATP	0.220±0.086	0.055-0.350	0.345±0.144	0.068-0.578
PCr/γATP	4.69±0.44	4.13-5.40	5.05±0.23	4.53-5.46
PCr/Pi	10.3±2.2	7.7-13.5	10.3±1.3	7.6-12.1
pH	6.97±0.01		6.98±0.02	

DISCUSSION

Despite the absence of myalgia in the statin group, the elevation of muscle PDE observed in this group vs. controls is greater than the elevation reported in muscle of fibromyalgia patients (22%, ref 3). Because of the wide (and unexplained) variability in muscle PDE content between human subjects, and the low incidence of clinically-recognized statin myopathy, a small cross-sectional study cannot establish a link between PDE content and statin-induced myopathy. Anecdotally however, we observed among the highest muscle PDE/γATP ratios (0.53) in one subject (a 33 yr old male, not included in the above group) who had stopped statin treatment 1 month earlier because of muscle pain and elevated serum CK (Fig. 4). Thus, a larger prospective study of changes in muscle PDE content with statin use seems warranted.

REFERENCES:

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FIG 1

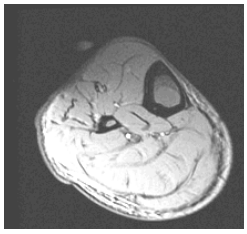

FIG. 2 (Control, 57 yr male)

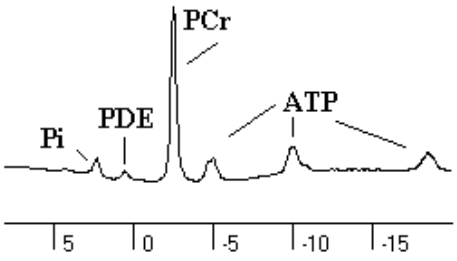

FIG. 3 (Statin, 57 yr male)

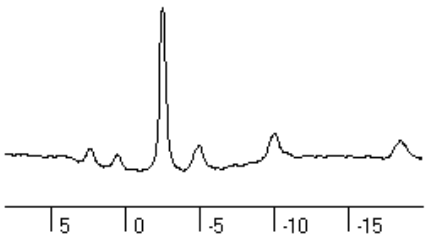

FIG. 4 (Statin 33 yr male)