Association between statin-associated myopathy and skeletal muscle damage

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The full-text version of this article is available at www.cmaj.ca/cgi/content/full/cmaj.081785

Abstract

Background: Many patients taking statins often complain of muscle pain and weakness. The extent to which muscle pain reflects muscle injury is unknown.

Methods: We obtained biopsy samples from the vastus lateralis muscle of 83 patients. Of the 44 patients with clinically diagnosed statin-associated myopathy, 29 were currently taking a statin, and 15 had discontinued statin therapy before the biopsy (minimal duration of discontinuation 3 weeks). We also included 19 patients who were taking statins and had no myopathy, and 20 patients who had never taken statins and had no myopathy. We classified the muscles as injured if 2% or more of the muscle fibres in a biopsy sample showed damage. Using reverse transcriptase polymerase chain reaction, we evaluated the expression levels of candidate genes potentially related to myocyte injury.

Results: Muscle injury was observed in 25 (of 44) patients with myopathy and in 1 patient without myopathy. Only 1 patient with structural injury had a circulating level of creatine phosphokinase that was elevated more than 1950 U/L (10× the upper limit of normal). Expression of ryanodine receptor 3 was significantly upregulated in patients with biopsy evidence of structural damage (1.7, standard error of the mean 0.3).

Interpretation: Persistent myopathy in patients taking statins reflects structural muscle damage. A lack of elevated levels of circulating creatine phosphokinase does not rule out structural muscle injury. Upregulation of the expression of ryanodine receptor 3 is suggestive of an intracellular calcium leak.

Statins are among the most widely prescribed medications worldwide. Although their overall safety profile is excellent, myalgia without functional muscle impairment commonly affects patients taking statins. The clinical manifestations of statin-associated myopathy include pain and muscle weakness. Observational studies have shown a myalgia rate of 10%–15% among patients taking statins. Fulminant and potentially fatal rhabdomyolysis may also occur. Myalgia is typically considered by patients and physicians to be a minor adverse effect. Current consensus guideline support continuation of the statin therapy as long as circulating levels of creatine phosphokinase are less than 1950 U/L (10× the upper limit of normal). We sought to determine whether statin-associated myopathy is associated with underlying structural muscle damage.

Methods

The full methods are available in the full-text version (available at www.cmaj.ca/cgi/content/full/cmaj.081785).

Samples of the vastus lateralis muscle were collected from 83 people in 5 groups. The first control group comprised 10 healthy male volunteers who had never taken statins and who had no muscle complaints. (Biopsy samples from these patients were obtained during a previous study). The second control group consisted of 10 patients who were age-matched to patients in the myopathy group. These patients had never taken statins. The third group comprised 15 patients who had a history of clinically diagnosed statin-associated myopathy. These patients had discontinued their statin treatment for a minimum of 3 (median 12) weeks before the biopsy. The fourth group consisted of 29 patients who had clinically diagnosed statin-associated myopathy and were taking a statin at the time of biopsy. The fifth group consisted of 19 patients who were taking statins and who had no muscle complaints.

Patients were identified as having statin-associated myopathy by clinical criteria consistent with the recommendations of the Muscle Safety Expert Panel. The vastus lateralis muscle was biopsied at mid-thigh level.
Tissue processing
The tissue was processed for electron microscopy, ultracytome-
tomy and immunohistochemistry as previously described.9,10

RNA isolation and gene expression studies
We isolated total RNA from the muscle biopsy samples and
synthesized cDNA. We analyzed the expression of 8 genes
that code for proteins situated in the T tubule region and that
are involved in the regulation of intracellular calcium homeo-

Tissue analysis
The number of muscle fibres with structural abnormalities
was expressed as a percentage of the total number of fibres
per section under a light microscope. We arbitrarily defined

Table 1: Characteristics of patients included in a study of the relation between statin-associated myopathy and structural muscle damage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group 1† (n = 10)</th>
<th>Control group 2† (n = 10)</th>
<th>Former statin users with myopathy (n = 15)</th>
<th>Current statin users with myopathy (n = 29)</th>
<th>Current statin users with no myopathy (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>0</td>
<td>30</td>
<td>47</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>Age, yr, mean (range)</td>
<td>26 (23–29)</td>
<td>57 (41–74)</td>
<td>59 (34–73)</td>
<td>54 (34–76)</td>
<td>66 (49–84)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, median (IQR)</td>
<td>ND</td>
<td>6.2 (2.34)</td>
<td>6.5 (2.70)</td>
<td>5.0 (1.12)</td>
<td>5.4 (1.44)</td>
</tr>
<tr>
<td>HDL, mmol/L, median (IQR)</td>
<td>ND</td>
<td>1.84 (0.89)</td>
<td>1.58 (0.70)</td>
<td>1.6 (0.58)</td>
<td>1.5 (0.64)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L, median (IQR)</td>
<td>ND</td>
<td>2.62 (2.09)</td>
<td>2.5 (5.34)</td>
<td>2.45 (3.35)</td>
<td>2.1 (1.79)</td>
</tr>
<tr>
<td>LDL, mmol/L, median (IQR)</td>
<td>ND</td>
<td>4.2 (0.90)</td>
<td>5.15 (3.68)</td>
<td>2.9 (1.10)</td>
<td>3.2 (1.30)</td>
</tr>
<tr>
<td>CPK, U/L</td>
<td>ND</td>
<td>110 (250)</td>
<td>114 (117)</td>
<td>118 (424)</td>
<td>109 (44.5)</td>
</tr>
<tr>
<td>&gt; 975 U/L (5× ULN)</td>
<td>ND</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt; 1950 U/L (10× ULN)</td>
<td>ND</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
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<tr>
<td>Active statin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Simvastatin</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (41)</td>
<td>15 (74)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (31)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
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<td></td>
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<td>1 (5)</td>
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<tr>
<td>Pravastatin</td>
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<td>8 (53)</td>
<td>5 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cerivastatin</td>
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<td>0 (0)</td>
<td>1 (7)</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>No. (%) of muscle fibres damaged; [range, %]</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (60) [2.8–100]</td>
<td>9 (60) [3.3–43]</td>
<td>1 (5)</td>
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<td>Concomitant medication use</td>
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<td></td>
<td></td>
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<td></td>
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<td>Fibrates</td>
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<td>0 (0)</td>
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<td>Immunosuppressants</td>
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<td>2 (20)</td>
<td>5 (33)</td>
<td>14 (48)</td>
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<tr>
<td>Corticosteroids</td>
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<td>3 (33)</td>
<td>5 (33)</td>
<td>9 (31)</td>
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</tr>
<tr>
<td>Warfarin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>1 (3)</td>
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<tr>
<td>Macrolid antibiotics</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>1 (7)</td>
<td>2 (7)</td>
<td>None</td>
</tr>
<tr>
<td>Antifungals</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>None</td>
</tr>
<tr>
<td>HIV-protease inhibitors</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>None</td>
</tr>
</tbody>
</table>

Note: CPK = creatine phosphokinase, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, ND = not determined, ULN = upper limit of normal.
*Unless otherwise indicated.
†Patients with no history of statin use or muscle complaints.
‡Patients with no history of statin use or muscle complaints. These patients were age-matched to patients with myopathy.
the threshold for significant muscle injury as 2% or greater damaged fibres per biopsy sample.

Statistical analysis
The data are expressed as mean and standard error of the mean (SEM). We compared the prevalence of muscle injury in the groups by use of the Fisher exact test. We performed multiple group comparisons for categorical variables by use of nonparametric analysis of variance by ranks. For continuous variables, we performed an analysis of variance followed by the Dunn multiple comparison test. We evaluated correlations between the circulating level of creatine phosphokinase and the extent of injury using the Pearson correlation coefficient. For mRNA expression analysis, we evaluated the normality by use of the Kolmogorov–Smirnov test (α = 0.05), with the Lilliefors significance correction. Because the expression of the genes did have a normal distribution, we performed a Mann–Whitney U test. The level of significance was set at p < 0.05.

Results
Most of the patients with statin-associated myopathy were men with moderate hypercholesterolemia (Table 1). The average age was 56.5 years. Simvastatin and pravastatin were the most commonly reported statins used, and 25% of patients had taken more than 1 statin.

The risk of developing statin-associated myopathy has been reported to be exacerbated by a number of drugs that interfere with the metabolism of statins.11–14 Because patients in our study were middle-aged and had multiple comorbidities, most were taking several drugs. About 40% of all patients with myopathy were taking corticosteroids or immunosuppressants, or both. Therefore, we include an age-matched control group of 10 patients who were not taking statins but were taking other medications, which were also matched to those in the myopathy group (Table 1).

Myopathy
Patients with myopathy reported weakness that was generally slight. They reported having difficulty rising from a chair without arm support. Muscle pain was reported predominately in the trunk and proximal muscle groups and was exacerbated by exercise. Patients reported that their symptoms were severe enough to interfere with the activities of daily living and that they had decreased exercise capacity. The symptoms had lasted for several weeks. Typically, the symptoms disappeared within days after cessation of statin therapy. In 3 cases, the symptoms persisted after statin therapy had been discontinued for more than 1 month (Table 2). One patient, who presented with overt rhabdomyolysis (creatine phosphokinase 57 657 U/L), required admission to hospital for the management of muscle pain.

### Muscle injury
Significant muscle injury was observed among patients with myopathy and in 1 patient who was taking long-term statin therapy and who had no myopathy (Table 1). There was no significant damage in the fibres of control patients not taking statins. Significant muscle damage was observed in 9 of 15 patients with myopathy who had discontinued statin therapy and in 16 of 29 patients with myopathy currently receiving statin therapy (Table 1). Compared to control patients, those who currently (p < 0.001) or previously (p < 0.001) used statins had significantly more muscle damage. There was no significant difference in the amount of damage between patients currently and formerly taking statins (p = 0.90).

We found lesions in 3.3%–43% of the muscle fibres in the injured skeletal muscles from patients with myopathy currently taking statins and in 2.8%–100% of the muscle fibres from patients with myopathy who were former statin users (Table 1). In the injured muscles of patients with myopathy, the median percent of injured fibres was 9.5% (25%–75% confidence interval [CI] 5.1%–17.6%) among current statin users and 9.0% (25%–75% CI 3.3%–19.1%) among former statin users.

Of the 9 patients with significant muscle injury, 6 had stopped taking statins within 5–20 weeks, and 3 had stopped between 1 year and more than 5 years (median 12 weeks). The severity of muscle damage was not linearly correlated with length of statin therapy.

### Electron microscopy
Although damaged muscle fibres were widespread in most biopsy samples, the degree of destruction in individual fibres was modest. Representative images from the muscle biopsy samples from patients who had or had not taken statins are shown in Figure 1 of the full-text article (available at www.cmaj.ca/cgi/content/full/cmaj.081785). Light microscopy of semi-thin sections showed subsarcolemmal detachment of the contractile apparatus. Electron microscopy confirmed this finding and showed that the sarcolemma was undamaged. Occasionally, we observed ghost fibres, which

<table>
<thead>
<tr>
<th>Table 2: History of myopathy among patients who used statins</th>
<th>No. (%)* patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Former statin users with myopathy</td>
</tr>
<tr>
<td>Myalgia†</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Weakness in proximal limb muscle and trunk</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Cramps</td>
<td>2 (13)</td>
</tr>
<tr>
<td>No. of weeks since discontinuing statin use, median [range]</td>
<td>12 [3–300]</td>
</tr>
<tr>
<td>Continuation of symptoms* after statin withdrawal for &gt; 1 month</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Note: NA = not applicable.
*Unless otherwise indicated.
†Predominantly in the muscles of the proximal limbs and exacerbated with exercise.
‡Myalgia, weakness or cramps.
are hollow sarcolemmal tubes of degenerated cells. There was marked variations in the size of the fibres among patients with myopathy.

On examination of the semi-thin sections, we found extensive intracellular vacuolization in skeletal muscle from a patient with myopathy currently taking statins and a patient with myopathy who had discontinued statin therapy (Figure 1 of the full-text article, available at www.cmaj.ca/cgi/content/full/cmaj.081785). The muscle fibres from patients in the control groups showed no vacuolization.

The intracellular vacuoles correspond to membranous cavities, as shown by electron microscopy. Labelling with an antibody against annexin A6, a T-tubular marker protein, showed that the distribution of these vacuoles was consistent with the T tubule system\(^5\) (Figure 2 of the full-text article, available at www.cmaj.ca/cgi/content/full/cmaj.081785).

**Gene expression**

We focused our gene expression analysis on the expression of genes that code for proteins that localize to T tubules or the sarcoplasmic reticulum and that are involved in calcium release or uptake. The expression of each gene was normalized to the amount of 18S RNA in the sample. Shown are the mean values of significant muscle damage (squares, \(n = 32\)) or no significant damage (circles, \(n = 25\)). Of the patients with structural damage, 21 were currently taking statins. Thirteen of the patients without structural damage were taking statins. The expression of ryanodine receptor 3 mRNA was significantly higher among patients with structural damage than among those without damage (1.7, SEM 0.3, \(p = 0.039\); Figure 1 of this version). The expression of sarco-endoplasmic reticulum transporting Ca\(^{2+}\) ATPase 3 was also higher among those with structural damage than among those without damage (1.85, SEM 0.4, \(p = 0.51\); Figure 3). This trend was not statistically significant, likely because of the high degree of variability of sarco-endoplasmic reticulum transporting Ca\(^{2+}\) ATPase 3 expression.

There were no differences in expression of the inositol triphosphate receptor isoforms (inositol 1,4,5-triphosphate receptor, type 1, \(p = 0.45\); inositol 1,4,5-triphosphate receptor, type 2, \(p = 0.17\); inositol 1,4,5-triphosphate receptor, type 3, \(p = 0.99\)), ryanodine receptor 1 (\(p = 0.724\)) and sarco-endoplasmic reticulum transporting Ca\(^{2+}\) ATPase pumps 1 and 2 (sarco-endoplasmic reticulum transporting Ca\(^{2+}\) ATPase 1 \(p = 0.35\); sarco-endoplasmic reticulum transporting Ca\(^{2+}\) ATPase 2 \(p = 0.63\)) between patients with and without structural damage (Figure 3).

**Creatine phosphokinase**

The mean level of creatine phosphokinase was higher in patients with myopathy currently taking statins than in the other groups. With the exception of 1 patient who had rhabdomyolysis, the levels of creatine phosphokinase in the most patients with myopathy did not exceed 1950 U/L (Figure 2 of this version). On the basis of the level of creatine phosphokinase alone, we could not distinguish between patients who had and those who had not taken statins.

**Interpretation**

We found a high prevalence of muscle injury in patients with clinically evident statin-associated myopathy. In addition, we identified a typical histopathological appearance of statin-associated myopathy, characterized by vacuolization of the T-tubular system with intact sarcolemma. This damage can occur without increased levels of circulating creatine phosphokinase. Although muscle symptoms typically improve rapidly after stopping statin therapy, our findings suggest that some patients are more susceptible to statin-associated myotoxicity and persistent structural injury. These findings have several important clinical implications.

We were surprised to find structural muscle injury in patients who had discontinued statin therapy for a considerable time. In general, ces-
sation of treatment leads to alleviation of symptoms within days to weeks. However, because we identified patients on the basis of their history of statin-associated myopathy, we presumably selected for and identified a potentially vulnerable subgroup of patients who are prone to chronic structural lesions. We cannot exclude the possibility that these patients had an underlying myopathic process that was made evident by the use of statins.

Our findings call into question whether normal or mildly elevated levels of serum creatine phosphokinase can be used to exclude underlying and possibly ongoing muscle injury. Previous case reports have identified a small number of cases of statin-associated myopathy and pointed out the lack of a correlation between clinical symptoms and circulating levels of creatine phosphokinase. Our study adds to the previous observations by including larger numbers of patients and providing structural data from muscle biopsies.

In our study, the patients were taking a variety of statins, and all were given only moderate doses. We did not observe a correlation between higher doses of statins and a greater degree of muscle injury, nor did we see differences among the types of statins. No patient in our study was taking a high dose of statins (> 80 mg/day), which is often recommended. The risk of statin-associated myotoxic adverse effects is enhanced by concomitant use of some medications. All statins are biotransformed in the liver, and drugs that interfere with this process may raise or lower the levels of these products in the blood. Fibrates, warfarin, macrolid antibiotics, antifungal agents and immunosuppressants all predispose patients to myopathy. In our study, there was no correlation between the extent of muscle damage and the use of any other single drug with a statin. However, the number of patients in each subgroup was small, and none of the patients were taking fibrates.

Glucocorticoids are known to cause wasting of proximal skeletal muscles. In the prestatin era, a study from our laboratory showed ultrastructural changes in the skeletal muscle of renal-transplant patients taking immunosuppressants and who had steroid-induced myopathy. Although a diffuse decrease in myofibrils was observed in these patients, neither intracellular vacuolation nor subsarcolemmal detachment of myofibrils, as was observed in our current study, were seen.

We found that damage to the muscle fibres is largely restricted to the intracellular space, involving the T-tubular system. The intact lateral sarcolemma likely prevents leakage of creatine phosphokinase into the bloodstream. Vacuolization may be associated with increased vulnerability of the muscle fibre to mechanical injury. We have previously reported microscopic damage to skeletal muscle in asymptomatic patients taking statins, suggesting that statins may contribute to muscle damage. In our previous study involving asymptomatic patients, the characteristics of the damage were similar to that seen in patients with myopathy in the present study. However, the severity and prevalence of damage was considerably less in our previous study than that observed in the current population with myopathy and was well below our significance cutoff of 2% of fibres damaged. In the current study, only 1 asymptomatic patient had structural muscle damage greater than 2%.

Ryanodine receptor 3 is the predominant isoform of this receptor in fetal and neonatal skeletal muscle. Adult skeletal muscle always contains ryanodine receptor 1, and it may have variable amounts of ryanodine receptor 3. The mechanistic and diagnostic implications of our finding of increased expression of ryanodine receptor 3 expression remains to be determined. First, it is unclear whether the expression of ryanodine receptor 3 was upregulated before statin use or whether its expression was increased as a result of statin-induced muscle injury. If the expression was increased before development of statin-induced myopathy, this could have important implications. Increased expression of ryanodine receptor 3 could represent a potential defect in calcium homeostasis, which could result in myofibre damage in statin users. Thus, the overexpression of ryanodine receptor 3 could contribute to the skeletal muscle selectivity of statin-associated myopathy, because cardiac muscle expresses ryanodine receptor 2 but not ryanodine receptor 3.

Figure 2: Circulating levels of creatine phosphokinase in patients with statin-associated myopathy and current (myopathy current statin) or past (myopathy former statin) statin therapy and in age-matched patients currently using statins with no myopathy. Note: ULN = upper limit of normal.
Limitations
Our study has several limitations. First, patients were identified clinically as having statin-associated myopathy without clear criteria for what constitutes this clinical entity. In addition, these patients were not identified in a systematic manner. Therefore, the prevalence of underlying muscle damage among patients using statins and those with muscle-related complaints is unknown.

The small number of patients included in our study is also a limitation. However, we have included the largest series of cases studied by muscle biopsy. The small population size diminishes the power of this study to identify differences among patient groups and does not allow us to perform multivariable analyses. Thus, potential confounding factors could not be identified. The lack of longitudinal follow-up of these patients precludes us from determining what proportion of these patients will have their structural abnormalities resolve over time or with longer periods of cessation of statin therapy.

It also is likely that we underestimated the extent of muscle damage because all biopsies were taken from the vastus lateralis muscle, regardless of where the patient reported pain. Thus, it is possible that performing a biopsy of the affected muscle might have resulted in a higher prevalence of damage.

Conclusion
In current clinical practice, patients who present with muscle symptoms while receiving statin therapy have their creatine phosphokinase levels measured. If the level is within normal limits or is modestly elevated (current recommendations include creatine phosphokinase < 1950 U/L), patients are frequently advised to continue their current statin therapy. This is based on the assumption that a lack of increased creatine phosphokinase levels supports a lack of underlying muscle damage. Our findings suggest that normal or moderately elevated levels of creatine phosphokinase do not exclude statin-associated muscle injury. Thus, alternative treatment strategies for patients with muscle symptoms need to be evaluated.

This article has been peer reviewed.

Competing interests: Richard Karas has received honoraria from Merck. Annette Draeger received honoraria from Pharmaceutical Product Development from January to April 2008 for diagnostic counselling in a phase I study unrelated to this article.

No competing interests declared by Markus Mohaupt, Eduard Babiychuk, Verónica Sanchez-Freire, Katia Monastyrskaya, Lakshmanan Iyer, Hans Hoppeler or Fabio Breil.

Contributors: All of the authors contributed to the study design, developed the protocol and contributed to the drafting of the manuscript. Verónica Sanchez-Freire, Lakshmanan Iyer and Richard Karas provided statistical knowledge. Markus Mohaupt and Hans Hoppeler performed the muscle biopsies. Richard Karas contributed specific clinical knowledge. Annette Draeger conceived the study and drafted the manuscript. All of the authors revised it for intellectual content and approved the final version submitted for publication.

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