EFFECT OF PHYSICAL EXERCISE AND STATINS ON THE MUSCLE FUNCTION IN ANIMALS WITH DYSLIPIDEMIA

EXERCISE AND SPORTS SCIENCES

ORIGINAL ARTICLE

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ABSTRACT

Statins are used in the treatment of dyslipidemias with great tolerance; however, several side effects can arise, mainly myopathies. Regular practice of physical exercises (PE) produces beneficial alteration in the lipid profile, but it can result in muscular lesions. Objective: to evaluate the effect of the association between physical exercise and statins in the muscular function through histological analysis in an experimental animal model with dyslipidemia. Methods: 80 male Wistar mice, distributed in 8 groups, namely: animals submitted to a hypercholesterolemic diet (HD), simvastatin with (G1) and without PE (G2) ; HD and fluvastatin with (G3) and without PE (G4); fed with commercial food (CF) in the presence (G5) and absence of PE (G6); HD submitted (G7) or not (G8) to PE were used. The HD was administered statins and PE practice on treadmill for 90 days for 8 weeks. The animals were sacrificed, and the soleus muscle was removed for histological analysis. Paired t-tests and multivariate analysis were applied with significance level of $p<0.05$. Results: The most important histological alterations found were fibers with different diameters and atrophic, with degeneration, splitting, edema and inflammatory infiltrate. These alterations were observed in 90% of animals from G1; 80% from G2; 70% from G3; 30% from G4; 40% from G5 and 30% from G7. In the G6 and G8 groups muscular fibers with preserved morphology were identified. Conclusion: In the muscular histological evaluation, the association of fluvastatin, symvastatin and physical exercise results in morphological alterations with predominance with the use of simvastatin, varying from a light to a high level, in the soleus muscle of mice, induced by HMG-CoA reductase inhibitors.

Keywords: HMG-CoA reductase inhibitors, aerobic physical exercise, myopathy.

INTRODUCTION

Dyslipidemia is characterized by disturbs in the levels of circulating lipids with diverse clinical manifestations[1]. Its treatment usually includes eating adaptation, regular practice of physical exercise, associated or not with pharmacological treatment.

Statins are important pharmacological substances used in the treatment of dyslipidemia. They act in the inhibition of the HMG-CoA enzyme (hydroxymethylglutaryl coenzyme A) redutase, which regulates the intracellular and hepatic cholesterol production. This enzyme catalyzes the conversion of the HMG-CoA in mevalonic acid, a substrate for the cholesterol synthesis. The result is decrease of the cholesterol hepatic synthesis and increase of the synthesis of LDL receptors (B/E receptor) on the surface of the hepatocyte, with consequent increase of the low-density lipoprotein removal (LDL), decrease of their plasma levels and decrease of their intraluminal absorption[2]. Additionally, they interfere with the secretion of very low-density lipoprotein (VLDL), of intermediate-density lipoprotein (IDL) and apolipoprotein B, contributing hence to the reduction of the circulating LDL. Additionally, they induce to discreet increase in the HDL levels, probably for decreasing the activity of the cholesteryl ester transfer protein (CETP) and increasing the synthesis of apolipoprotein A-I[1].

Statins are well-tolerated by most of the patients; however, many collateral effects may appear, especially myopatia, which appears with symptoms including fatigue, weakness and muscle pain, followed or not by increase of the creatinephosphokinase muscle enzyme (CPK)[3]. Muscular injuries caused by the use of statins, may be light or severe, ranging from myalgia to rhabdomyolysis affecting five to 10% of the patients[4].

Regular practice of aerobic physical exercise induces to reduction in the triglyceride levels (TG), special increase in the cholesterol fraction of the high-density lipoprotein (HDLc), and benefic alterations in the chemical composition of its subfractions, with increase of HDL_{2-c} and decrease of $HDL_{3-c.}$ Moreover, it is associated with increase of the activity of the lipoprotein lipase (LPL) and lecitin-cholesterol aciltransferase (LCAT) enzymes and reduction in the CETP activity. Therefore, physical exercise affects the lipoproteins metabolism, influencing on the cholesterol reverse transport as well as the TG-rich lipoproteins metabolism[5]. These effects may be intensified when associated with low-fat diet, especially saturated ones, decrease in body weight and reduction of adiposity[6].

Conversely, the levels of the LDL cholesterol fraction (LDLc) are resistant to physical training, which seems to reduce the oxidized LDL level though, offering lower risk for atherosclerosis[7].

Although physical training induces to beneficial adaptations, performance of exercises which involve eccentric actions above the habitual exertion intensity usually results in muscular injury[8]. In that case, ultra-structural injuries, sarcolemma rupture[9] and increase of the serum activity of muscular enzymes such as creatine phosphokinase (CPK) and lactate dehydrogenase[10] are evidenced. Besides that, there is reference of the increase of macrophages, monocytes and neutrophils which have also observed in response to the intense exercise[9]. Therefore, this study had the aim to evaluate the effect of the association between physical exercise and statins in the muscular function, by the histological analysis, in animal experimental model with dyslipidemia.

METHODS

This study followed the ethical procedures required, with approval of the Ethics in Animal Experimentation Committee (CEEA) of the Medicine College of São José do Rio Preto – CEEA-FAMERP (file number 5363/2005).

80 male Wistar rats (*Rattus novergicus*), randomly selected, mean weight of 272.9 ± 26.68g, kept in plastic cages with four animals, which remained in the animal facility of the Histology Laboratory of the Sciences and Technology College of the UNESP of Presidente Prudente, with mean temperature of 22 ± 2°C, humidity of 50 ± 10%, and 12-hour light/dark cycle with beginning of the light cycle at 7:00 o'clock were used. Food and water were provided *ad libitum* and daily changed.

According to the kind of diet, the administration of the hypolipidemic drug, performed by force-feeding, and physical exercise practice, the animals were randomly distributed in eight groups identified as follows:

- Group 1 (G1) – 10 animals submitted to the hypercholesterolemic diet for 90 days with administration of hypolipidemic drug (simvastatin) and performance of physical exercise on treadmill, both during eight weeks.
- Group 2 (G2) – 10 animals submitted to the hypercholesterolemic diet for 90 days with administration of hypolipidemic drug (simvastatin) during eight weeks**,** kept sedentary.
- Group 3 (G3) – 10 animals submitted to the hypercholesterolemic diet for 90 days with administration of hypolipidemic drug (fluvastatin), with performance of physical exercise on treadmill, both during eight weeks.
- Group 4 (G4) – 10 animals submitted to the hypercholesterolemic diet for 90 days with administration of hypolipidemic drug (fluvastatin) during eight weeks and kept sedentary.
- Group 5 (G5) – 10 animals submitted to the diet with commercial food (Purina) for 90 days, with performance of physical exercise on treadmill during eight weeks.
- Group 6 (G6) – 10 animals submitted to the diet with commercial food (Purina) for 90 days and kept sedentary.
- Group 7 (G7) – 10 animals submitted to the hypercholesterolemic diet for 90 days, with performance of physical exercise on treadmill during eight weeks.
- Group 8 (G8) – 10 animals submitted to the hypercholesterolemic diet for 90 days, kept sedentary.

The hypercholesterolemic diet was based on the AIN-93 with addition of starch (290g/kg), dextrin starch (155g/kg), commercial casein (175g/kg) sucrose (100g/kg), cellulose (50g/kg), coconut oil (120g/kg), soy oil (47.5g/kg), cholesterol (12.5g/kg), mineral mixture (35g/kg), vitamin mixture (10g/kg), L-cystine (1.8g/kg), choline birtratate (2.5g/kg) and tert butylhydroquinone (0.014g/kg)[11].

The drug dosing was calculated by allometric extrapolation[12] which is based on the metabolic rate of the animal. Due to the animals' size and body weight alteration, the drug dose was weekly recalculated, and the initial dose ranged from 0.31 to 0.53mg.

The training program was performed on treadmill for small animals, keeping velocity at 9.75m/min, with a total of 585m at each 60-minute session, characterizing low intensity exertion. The exercise experimental protocol used comprehended two phases: adaptation – with daily gait sessions on treadmill with progressive duration during the 10 first days; and training phase – daily sessions of 60 minutes of gait, five days per week, during eight weeks[13]. After the training period, the animals were euthanized by the chemical method. Afterwards, surgical method for removal of the soleus muscle of the right pelvic muscle was performed. The samples of the soleus muscle venter, measuring approximately 2.0cm long and 0.5cm of diameter, with the longitudinal fibers displayed on the bigger axis of the length, were frozen by immersion in n-hexane, refrigerated at –70°C in liquid nitrogen by freezing of the non-fixed and stored tissue[14] in nitrogen storage tank. The muscle fragments were sectioned using semi-seriate cuts of 8µm with acquisition of three cuts at every 50µm, obtained by microtome cryostat HM 505 E Microm, –20°C. The histological analysis was performed with staining of the material with hematoxylin and eosin (HE)[14], for evaluation of the following characteristics: general fascicular architecture of the musculature, size and shape of the fibers, position and number of nuclei in the cell, inflammatory processes and cytoplasmic basophilia, according to the methodology previously described in the literature[15]. The photographic documentation of the microscopic aspects was performed with the aid of image digitalization system, constituted by a Leica DMRX (self-software) optical microscope, with increase of 50x/0.75 in the objectives and 10x/22 in the ocular and a Pentium III computer attached to a digital camera.

Qualitative analysis was used, considering morphological evaluations of the muscle, and quantitative by multivariate analysis. In that case, analysis of main components was applied for determination of association factors between the histological parameters: peripheral nucleus, splitting (longitudinal division process), inflammatory infiltrate, fiber under degeneration (necrosis), atrophic, edema, rounded fiber, endomysium, perimysium and fascicular pattern. Analysis of variance (ANOVA)[16] was performed observing the Factor 1, characterized by the presence of the peripheral nucleus contrasting with the presence of splitting, inflammatory infiltrate, fiber under degeneration, atrophic, edema, rounded fiber, endomysium, perimysium and fascicular pattern. Error at 5% was accepted with significance level for value $p<0.05$.

RESULTS

The histological analysis of the soleus muscle presented muscle fibers with preserved morphology including polygonal aspect, different diameters and peripheral nuclei in all animals from the sedentary control groups (G6 = commercial food and sedentarism and G8 = hypercholesterolemic diet and sedentarism). The fibers were organized in fascicles by the perimysium and each fiber surrounded by the endomysium and each fiber surrounded by the endomysium (figures 2B and 2D). However, in the soleus muscle of the animals submitted to physical exercise associated with commercial food (G5; figure 2A) or the hypercholesterolemic diet (G7; figure 2C) muscular fibers of different diameters (polymorphic, angle, rounded, triangular), with edema, under degeneration (necrosis), with longitudinal division process (splitting) and cells of conjunctive cells with inflammatory infiltrate in 40% and 30% of the animals, were respectively identified. On the other hand, in the group submitted to the hypercholesterolemic diet, simvastatin and sedentarism (G2; figure 1B) fibers of different diameters were observed (polymorphic, angle, triangular, rounded) and presence of edema and conjunctive tissue with inflammatory infiltrate in 80% of the animals, while in G4, whose animals were treated with the same diet, were also kept sedentary, but with association of fluvastatin, fibers of different diameters were observed (polymorphic, angular, triangular, atrophic), under degeneration, splitting, and cells of conjunctive tissue with inflammatory infiltrate in 30% of the animals (figure 1D). The group treated with hypercholesterolemic diet, hypolipidemic and physical exercise, fibers of different diameters (polymorphic, angular, triangular, rounded), atrophic, with longitudinal division process (splitting) and cells of the conjunctive tissue with inflammatory infiltrate were observed in 90% of the animals in G1 and 70% in G3 (figures 1A and 1C, respectively).

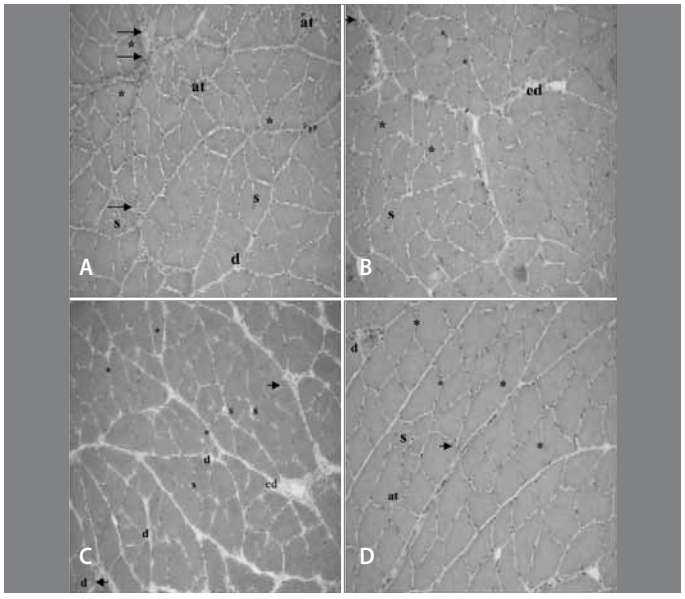

Figure 1. Transversal section of the soleus muscle of Wistar rat. A – Group 1: hypercholesterolemic diet + simvastatin + physical exercise; B - Group 2: hypercholesterolemic diet + simvastatin + sedentarism; C - Group 3: hypercholesterolemic diet + fluvastatin+ physical exercise; D – Group 4: hypercholesterolemic diet + simvastatin + sedentarism. Observe * = fibers of different diameters (polymorphic, angular, triangular, rounded); d = under degeneration (necrosis); at = atrophic; s = splitting (longitudinal division process); → = cells of the conjunctive tissue with inflammatory infiltrate; ed = edema. HE 50 X.

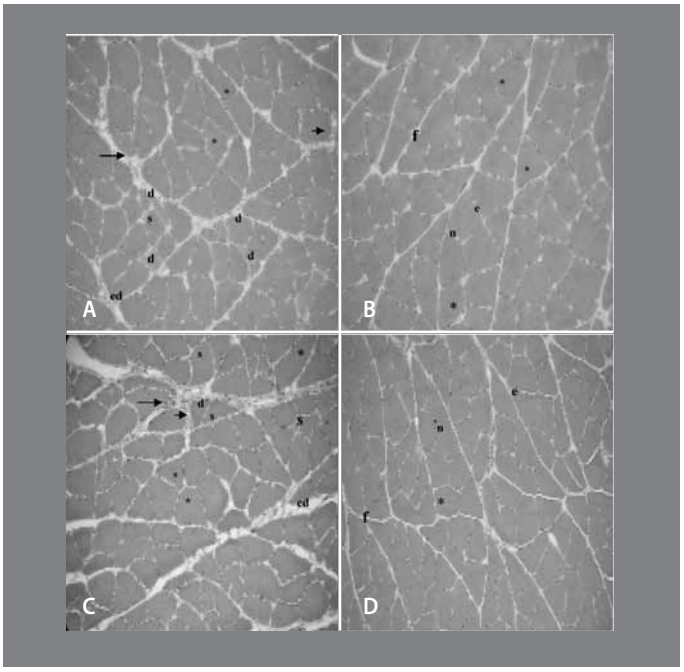

Figure 2. Transversal section of the soleus muscle of Wistar rat. A – Group 5: commercial food + physical exercise; B – Group 6: commercial food + sedentarism; C - Group 7: hypercholesterolemic diet + physical exercise; D - Group 8: hypercholesterolemic diet + sedentarism. Observe * = fibers of different diameters (polymorphic, angular, triangular, rounded); d = under degeneration (necrosis); s = splitting (longitudinal division process); → = cells of conjunctive tissue with inflammatory infiltrate; ed = edema; f = fascicular pattern; n = peripheral nucleus; e = endomysium. HE 50 X.

The analysis of the main components defined based on the histological aspect, a first factor (Factor 1) which explained 30% of total histological variation, represented by the presence of the peripheral nucleus in contrast with presence of splitting (longitudinal division process), inflammatory infiltrate, fiber under degeneration (necrosis), atrophic, edema, rounded fiber, endomysium, perimysium, fascicular pattern. Figure 3 presents the list of the main components with the treatments of the groups. Lower frequency of peripheral nuclei and prevalence of splitting (longitudinal division process), inflammatory infiltrate, fiber under degeneration (necrosis), atrophic fiber, edema, rounded fiber, endomysium, perimysium, fascicular pattern, highlighting between groups, but without significant difference (value $p < 0.05$), represented by the intersection of their respective confidence intervals (figure 3) were observed in the groups submitted to the hypercholesterolemic diet, simvastatin with or without physical exercise (G1 and G2, respectively) .

In that case, when relating the Factor 1 with the kind of treatment, lower frequency of peripheral nuclei was observed in the group treated with hypercholesterolemic diet, fluvastatin and physical exercise (G3) in contrast with the higher frequency of the other histological characteristics already mentioned, being different from the groups with hypercholesterolemic diet associated with physical exercise (G7), sedentarism with administration of fluvastatin (G4), and commercial food with (G5) or without (G6) physical exercise ($p < 0.05$), represented by the absence of intersection of their respective confidence intervals (figure 3).

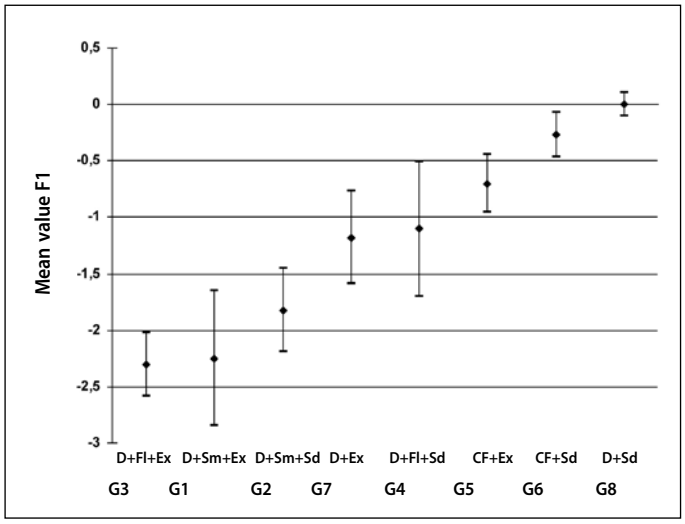

Figure 3. Distribution of the mean values obtained in the analysis of main components, considering the studied groups. This graphic representation identifies the groups according to the histological pattern, concerning Factor 1 (presence of peripheral nucleus contrasting to the presence of splitting, inflammatory infiltrate, fiber under degeneration (necrosis), atrophic, edema, rounded fiber, endomysium, perimysium, fascicular pattern, which explains 30% of the total variation of the histological profile. The values, the closer to zero, the more indicate lower level of muscular injury.

DISCUSSION

In this study, we can highlight in the histological analysis of the soleus muscle of animals under statins treatment associated or not with the practice of physical exercise, the presence of splitting, which characterizes the longitudinal division of the muscle fibers or the incomplete fusion of satellite cells proliferated after the injury of the muscle fibers. This condition may be the indication of presence of hyperplasia[15].

Many triggering factors to these alterations have been proposed, with special attention to high level of stress caused by the exercise, the metabolic stress and the alterations in the microcirculation[17]. Moreover, rounding processes of the fibers and the presence of necrosis and inflammatory infiltrates, especially in the animals submitted to the diet with commercial food and physical exercise and hypercholesterolemic diet and physical exercise, also indicate the possibility of myopathic scenario. The diets applied in the present study independently, do not interfere in the histological parameters, corroborating the findings by Ciabattari *et al*.[18], who analyzed the effect of swimming associated with different diets on the tibialis anterior muscle of Wistar rat.

On the other hand, the use of hypolipidic drugs itself can in isolation, lead to muscular injury. Studies in individuals treated with statins evidenced muscle injuries even before physical exercise[19]. In the preset study, 80% of the animals treated with simvastatin and kept sedentary presented polymorphism of the muscle fibers, edema and conjunctive tissue with inflammatory infiltrate. In the group which performed the same treatment and practiced exercise, the mentioned muscle alterations occurred in addition to atrophic fibers and with longitudinal division process (splitting), in 90% of the animals. Bonfim *et al*.[20] submitted Wistar rats to the treatment with simvastatin and physical exercise and also detected in the histological analysis in the muscle injuries of the gastrocnemius muscle including splitting (frequency of 40%), atrophic fibers (frequency of 60%) polymorphism of the muscle fibers and inflammatory infiltrate, both with frequency of 100%. In the sedentary group with use of simvastatin the same histological alterations have been observed, but with lower frequency.

On the other hand, animals treated with fluvastatin and kept sedentary; despite presenting the histological findings similar to the group with simvastatin, occurred in only 30% of the animals. Nevertheless, in the group submitted to fluvastatin, but exercised, 70% of the animals presented muscular alterations and were similar to those observed in the animals under treatment with simvastatin and physical exercise. Franc *et al*.[19] also detected exacerbation of muscular injuries consequent of the use of statin associated to physical exercise. Such results suggest the presence of myopatia induced by the statins, being more frequent with the use of simvastatin and presenting exacerbation by physical exercise, for both hypolipidic drugs. However, there is reference that the hydroxy acid from fluvastatin may offer tissue selectivity, especially hepatic, with possibility to present lower muscular severity[21].

These results corroborate the research by Seachrist *et al*.[22], who investigated the muscular effects of the administration of cerivastatin associated to physical exercise on treadmill during two weeks. They observed muscle injuries, such as injuries in the sarcoplasma, internal nuclei, fibers degeneration, inflammatory infiltrate, being dose-dependent and more severe in the trained group. According to the authors, the results obtained indicated that the exacerbation of muscular injury observed did not occur as a consequence of the higher concentration of medication in the active musculature, but rather by the disturbed oxidative metabolism, since the mitochondrial injury was present.

The mechanisms through which the statins trigger muscular injury are not well-defined, and there are theories about the alterations in the excitability of the cellular membrane due to the decrease of the amount of membrane cholesterol; alterations in the cellular respiration caused by the reduction of the respiratory chain intermediate (ubiquinone – coenzyme Q10); and onset of apoptosis and by the increase of cytosolic calcium and consequently, activation of its signaling via mitocondrial[23,24]. The evidence in research indicates that the mitochondrial harm could probably interfere in the regulation of cytosolic calcium, leading to the onset of apoptotic and degenerative processes which would explain the muscular injuries by the statins[23,25]. In fact, some research points that the use of statins leads to mitochondrial injury, either being a primary or secondary factor in the muscular injury[26-28].

Moreover, in that context, many drugs, including statins, are excreted in the bile and urine. The renal excretion is the effect of the glomerular filtration, tubular secretion and tubular reabsorption. Thus, the glomerular filtration rate depends on the quantity of blood in the kidneys[29]. During physical exercise decrease in the renal blood flow is observed, which can decrease the glomerular filtration to as much as 30%. It is also possible that since physical exercise increases the blood flow in the muscle it leads to higher concentration of the drug in the muscular tissue and subsequent toxicity, being it a dose-dependent mechanism[30].

In the present study, edema, splitting and cells of the conjunctive tissue with inflammatory infiltrate in 40 and 30% of the animals, respectively was identified in the groups submitted to physical exercise associated with commercial food (G5) and the hypercholesterolemic diet (G7). Bonfim *et al*.[20] also identified muscular alterations in the gastrocnemius

muscle, with special attention to inflammatory infiltrate in all animals treated with commercial food and physical exercise. Actually, physical exercise per se only leads to injuries in the skeletal musculature, which on its turn, cause adaptive process, altering both shape and structure of the muscle fibers, as well as promoting inflammatory response[14,18].

In the muscular histological evaluation, considering the association between fluvastatin, simvastatin and physical exercise, it is concluded that it leads to morphological alterations with predominance in the use of simvastatin, ranging from light to severe level in the soleus muscle of rats, induced by the HMG-CoA redutase inhibitors.

All authors have declared there is not any potential conflict of interests concerning this article.

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