ABSTRACT

Introduction: Studies on the effect of statins on muscle strength are contradictory, with meager evidence of the influence in physical activity on the pattern of muscle contraction of its users. Objectives: The objective of the study was to verify the effect of physical activity practice on the force-time curve of handgrip. Method: For this purpose, 40 women (50-75 years) on statins (≥4 months), divided into Statin Sedentary Group (SSG, n = 13), Statin Exercise Group (SExG, n = 13) and Exercise Group (ExG, n = 14), the biochemical profile, body composition and handgrip strength-time curve were evaluated. Results: The results indicated a significant difference in time to achieve peak force (TFP) between the groups with and without statins (SExG = 2.8 ± 1.0 and GES = 2.5 ± 1.1 vs GEx = 1.5 ± 0.7), and the percentage of force loss (% FL) between the groups exercised (SExG = 7.8 ± 5.8 vs ExG = 24.4 ± 20.3). There was a significant correlation between exposure to statins and PFT values (r = 0.549), as well as % PF (r = 0.422); There was a moderate and significant inverse correlation between % PF versus PFT (r = -0.568), and between % PF versus final force (r = -0.603). Conclusion: The results suggest that statins may interfere with the values of the hand grip Force-time curve, and physical activity may contribute to attenuate the side effects of the muscle contraction pattern caused by regular use of this medication.

Keywords: Physical activity. Muscle strength. Hydroxymethylglutaryl-CoA reductase inhibitors.
INTRODUCTION

Statins are considered first-line drugs in the treatment of lipid disorders. Although well tolerated by most patients, they are related to the occurrence of hepatic and, mainly, muscular effects [1]. In general, muscle discomfort manifests as pain, cramp and / or muscle stiffness, but changes in tissue structure can be identified even in the absence of these reports; these effects may negatively affect the performance of daily activities, and the evidence of the effect of statins on the behavior of muscle strength is still contradictory [2-4].

A randomized clinical trial for use of atorvastatin (80mg/dl) or placebo for six months in a double-blind design found that despite the increased incidence of myalgia among treated individuals, drug use did not result in changes in muscle strength measurements [3]. Other studies that assessed muscle strength in subjects treated with statins identified both the absence of drug influence in this variable [5, 6], as well as positive [7] or negative effects [8].

These results, in addition to being inconsistent, indicate the effect of statins on absolute values of maximal strength, disregarding the force profile obtained in the force-time curve of contraction, which is particularly relevant in investigations of muscular disorders [9].

Considering the muscular and metabolic adaptations resulting from the practice of physical activities, which could be related to the reduction or attenuation of the muscular lesions associated with statins, as well as their function improvement [10, 11], it is relevant to identify their influence on the muscle strength profile of your users. Thus, the objective of the present study was to verify the effect of regular practice of physical activities on the parameters of the force-time curve of hand grip of women in regular use of statins.

METHODS

Sample

It consisted of 40 healthy postmenopausal women 50 to 75 years of age, who dyslipidemic and who had been receiving statins for at least four months. Patient recruitment was carried out at two Basic Healthcare Units (BHU), as well as two University Extension Projects developed by the Department of Physical Education of the Universidade Estadual Paulista (UNESP), Campus of Bauru, São Paulo [12]. The women were divided into three groups: i) Statistin Sedentary Group [SSG], n=13; ii) Statistin Exercise Group [GEEx], n=13; e, iii) Exercise Group [ExG], n=14.

The procedures used in this research obeyed the Criteria of Ethics in Research with Human Beings, according to resolution n. 196/96 of the National Health Council - Brasilia - DF, and were approved by the Ethics Committee of the Faculty of Sciences of the State University of São Paulo (UNESP) number 5252/2011.
Physical Activity Level

The level of habitual physical activity was obtained by applying the Baecke questionnaire, translated and validated by Florindo, Latorre [13], which was applied in the form of an interview; the participants were classified as active or sedentary, with participants being <180 minutes per week (3-4 hours/week) of moderate or vigorous physical activity in the last four months (4 months).

Profile Biochemist

For blood collection, participants were instructed to maintain fasting for 12 hours, avoid vigorous physical activity for 24 hours, and alcohol intake for 72 hours before blood collection.

Serum levels of Total Cholesterol (CT), High Density Lipoprotein (HDL-c), Low Density Lipoprotein (LDL-c) and Triglycerides (TG) were evaluated for the lipid profile. For these parameters the automated colorimetric enzymatic method was used. Serologic levels of total Creatine Kinase (CK) were used as markers of muscle injury, and liver responses were assessed by the serological measurement of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST). For these parameters an automated ultraviolet technique was used.

Body Composition

Body Mass (BM) and Height (H) measurements were used to analyze the body composition, which were used to calculate the Body Mass Index (BMI = Kg/m²) and the participants' classification under eutrophic conditions Kg/m2), and overweight (≥ 30 kg/m² ≤ BMI ≤ 29.9 kg/m²) and obese (≥ 30 kg/m²); the Waist Circumference (WC), being considered indicators of central obesity values ≥88 cm; the measurements of lean mass, body fat and percentage of fat were obtained by Dual-energy X-ray absorptiometry (DXA) with full body scanning of the brand HOLOGIC Discovery Wi (Hologic inc, Waltham, MA, USA).

Test of Hand Grip Strength

The muscle function of the patients was evaluated by hand grip strength. The maximal isometric handgrip strength was measured in a single maximal repetition of static contraction in the dominant hand, measured by a digital dynamometer (resolution of 0.1 Kgf or 1 N; total capacity of 100 Kgf or 1000 N) with load cell, coupled to a data capture systems (N2000 Pró-CEFISE®, Brasil). his system allows obtaining the force-time grip curve, which provides a broad spectrum of variables that occur between the beginning and end of the grip [14].

The following parameters were obtained from the force-time curve: i) Peak Force (PF), demonstrates the highest obtained value of force in relation to the time, and time to reach peak force (TPF), it demonstrates the acceleration time required to reach the maximum force; ii) 90% of peak force (90%PF) and time to reach
90% of peak force (T90%PF); iii) mean strength comprises the integral of the force curve acquired over the test divided by time (MP); iv) Final Force (FF), the value obtained at the final moment of the test; v) percentage of force loss, which comprises the percentage difference of force between the maximum peak acquired and the value at the final moment of the test (%FL); vi) Peak rate of rising force (PRRF), the capture of the force values are given every 0.1 seconds, in this sense this variable demonstrates the moment with the greatest acceleration, resulting in the best moment of force in relation to the time; Time (TPRRF) and Force (FPRRF) relative to the peak of rising force development (PRRF); vii) Total work (TW), that is, the integral of the total area of the force curve obtained., illustrated in figure I.

**Experimental Hand Grip Protocol**

The hand grip dynamometry test was performed standing, arms extended along the body, legs apart and aligned with the shoulders and semi-flexed knees. After detailed guidance, participants were asked to apply the maximum force as fast as possible, shortly after the beep of the device, with the contraction being maintained for five seconds. Verbal stimulation was offered throughout the contraction time.[14]

Three trials were performed, with a two-minute interval between evaluations; the curve of the highest maximum force value was considered for analysis. To exclude the individual reaction time effect after the test start signal, the minimum value of two kilograms / force (equivalent to 15 Newtons) has been set to begin recording the test variables. For the analysis of the data, the results obtained in the initial 4.5 seconds of the test were considered, in order to identify the responses at the moments of contraction.
Data Analysis

The data were organized in descriptive statistics, and the differences were identified by applying the Kruskal-Wallis test and Dunn’s post-hoc test; the Spearman correlation test was used to verify possible associations between the studied variables. The analyzes were performed in the statistical program SPSS 13.0 for Windows, adopting as significance level the value of p <0.05.

RESULTS

The general characteristics of the patients are presented in Table 1. Data analysis indicated no significant differences between groups, in the variables age, weight, height, body mass index and body composition variables; however, there was a greater occurrence of overweight and obesity in SSG (92,3%) e ExG (92,9%) compared to SExG (76,9%). Regarding the characteristics of the treatment with statins, only two classes of the drug were used, simvastatin (SExG: 69,2% e GES:100%) and atorvastatin (SExG: 30,8%); the dosages in use were not different between the medicated groups.

The table 2 shows the results of the biochemical parameters and the frequency of occurrence of altered parameters of the study groups. There were no significant differences in biochemical parameters between groups; the active women without medication (ExG) had higher triglyceride values compared to those of the SSG. The groups exposed to the drug showed lower occurrence of altered lipid parameters, but higher frequencies of alterations in the biomarkers of muscle and liver injury.
Regarding the results of the hand grip force-time curve parameters, data analysis indicated a statistically significant difference in time to reach peak force (TPF), which was higher in the groups with or without exercise. The percentage of force loss (% FL) was statistically lower in the SExG compared to the ExG. Although there are no significant differences between the groups in the other variables, it can be observed that GEEEx participants take longer to reach peak force, but lose a lower percentage of strength when compared to SSG and ExG patients (table III).

### Table 2. Biochemical parameters (mean ± standard deviation) and frequency of occurrence of altered parameters (%) in the groups studied.

|        | SExG (n=13) | SSG (n=13) | ExG (n=14) |
|--------|-------------|------------|------------|
| TC     | 167.8±34.8  | 166.2±37.5 | 172.6±45.5 |
| HDL-C  | 47.4±7.5    | 45.8±18.0  | 49.8±9.2   |
| LDL-C  | 115.2±32.0  | 124.5±32.1 | 129.3±32.3 |
| TG     | 139.5±62.1  | 125.9±40.3 | 182.1±47.8 |
| CK     | 21.1±4.9    | 103.0±52.5 | 99.1±41.7  |
| GOT    | 26.1±4.4    | 21.1±4.9   | 19.0±5.2   |
| GPT    | 23.6±4.4    | 20.2±6.4   | 20.9±8.7   |

*Significant difference between SExG and SSG; **Significant difference between SExG and ExG; ***Significant difference between SSG and ExG. 'n=12'; 'n=10'. Legend – TC: total cholesterol; HDL-C: high density lipoprotein; LDL-C: low density lipoprotein; TG: triglycerides; CK: creatine kinase; GOT: glutamic oxaloacetic transaminase; GPT: Glutamate-pyruvic transaminase. Fonte: Bonfim et al.

### Table 3. Values of the manual grip force-time curve of the study participants.

| Variable     | SExG         | SSG          | ExG          |
|--------------|--------------|--------------|--------------|
| PF           | 220.5±39.6   | 219.3±54.6   | 210.5±28.9   |
| TPF          | 2.8±1.0°     | 2.5±1.1°     | 1.5±0.7°     |
| 90%PF        | 198.4±35.7   | 197.4±49.1   | 189.5±26.0   |
| T90%PF       | 1.1±0.7°     | 1.0±0.7°     | 0.7±0.4°     |
| FMed         | 179.7±30.4   | 169.9±51.9   | 147.5±54.0   |
| FF           | 202.7±34.6   | 169.9±51.9   | 161.0±48.4   |
| %FL          | 7.8±5.8°     | 18.0±17.9    | 24.4±20.3    |
| PRRF         | 503.4±211.9  | 456.9±224.2  | 598.9±249.1  |
| TPRRF        | 0.29±0.3     | 0.25±0.1     | 0.25±0.2     |
| FPRRF        | 104.4±31.7   | 98.2±36.8    | 114.4±33.1   |
| TW           | 844.4±180.0  | 875.3±246.4  | 815.2±129.8  |

*Significant difference between SExG and SSG; **Significant difference between SExG and ExG. Legend – PF: Peak Force; TPF: time to reach peak force; 90%PF: 90% of peak force; T90%PF: Time to reach 90% of peak force; FMed: mean force; FF: final force; %FL: percentage of force loss; PRRF: peak of rising force; TPRRF: Time to peak of rising force; FPRRF: peak force of force development rate; FF: final force; TW: total work.
The correlations between the force variables and the other analyzed variables are presented in table 4. The results showed a significant moderate correlation between the use of the drug and the time values to reach, both the peak force, and 90% of the peak force, in addition to the percentage loss of force. In addition, the lean mass presented a moderate and significant correlation with the values of final strength and the percentage of loss of strength. It was also verified that there was an inverse, moderate and significant relationship between the percentage of loss of strength and time to reach maximum strength ($r = -0.568, p=0.000$), as well as % FL and final strength ($r = -0.603, p=0.000$).

**DISCUSSION**

In this study, no significant differences were found in the body composition profile and biochemical variables between the studied groups, indicating the absence of additional effects in these variables in response to the association of statins and physical activity. The results of intervention studies indicate that the addition of physical activity to regular treatment by statins does not alter the lipid parameters of its practitioners $^{[15, 16]}$, contrasting with the significant reductions in CT and LDL-c identified when both therapies are initiated concomitantly, evidencing the action of the drug $^{[17, 18]}$. This allows to suppose that the long time of use of statins and the practice of physical activities for more than six months, would limit the identification of the action of the physical activity in this parameter.
With regard to body composition its association with physical activity and use of statins is still conflicting, being identified both the maintenance of the values \[15, 16\] and their reduction \[18\]. Among the factors associated with these responses, we highlight the characteristics of the exercises practiced, being observed changes in programs with higher weekly volume of aerobic activities or more intense exercises. Although patients performed an exercise program that met the recommendations of the American College of Sports Medicine (ACSM) \[19\], adding a high volume of aerobic activities, their intensity was maintained in mild to moderate.

However, it is worth mentioning that higher exercise intensities during the treatment with statins are directly related to the exacerbation of the muscle attacks by the drug \[11\], however, the magnitude of this relation, as well as its frequency of occurrence are still uncertain \[4\]. In this study, it was found that subjects who were exercised and using statins had a higher frequency of CK values above the normal range, the absolute levels of this marker were not different from the other groups, indicating that the magnitude of the increase was not relevant. Similar results were found by Coen, Flynn \[15\] who did not find significant increases in CK levels or reports of myalgia in response to moderate exercise, and by Panayiotou, Paschalis \[20\] who also observed an increase in CK but without an increase in pain indexes, and an increase in HDL and a reduction in LDL-c.

In general, it is estimated that approximately 5 to 10% of patients on statins use signs of myopathy due to their use \[1\], with serum creatine kinase (CK) being a possible marker. However, it is also common to observe patients with muscle complaints without elevation of CK, or even patients without complaints, but with increased CK values \[21\], which indicates inconsistency in the identification of the muscular alterations resulting from statins by the biochemical test in question. In this way, it can be stated that the use of CK levels for the verification of signs of muscular problems is a method that has reduced reliability, being essential the use of other non-invasive methods, such as self-report of pain and the measurement of strength muscular.

Another indicator of muscle injury is strength capacity, since its development is directly related to the structural conditions of the musculature. Regarding the influence of statins in this parameter, the results of the researches are not enough to affirm that the patients in treatment present a reduction in muscle strength, since they are quite contradictory. \[2, 4\]. The results of this study indicate that patients on statins, exercised or not, had similar peak values of healthy women of the same age group, suggesting no effect of the drug on absolute maximum strength. The results contrast with those found by Noyes and Thompson \[22\] in their review article, where eight studies related to muscle function in trained and untrained statin users were observed, therefore, it was observed that people with trained statin a
better muscular function when compared to non-active people also using statin.

However, in the case of studies of muscular strength in the presence of musculoskeletal disorders, the isolated obtaining of the maximum force is not enough to identify the particularities of each frame, since, aspects such as speed of generation of the force and its maintenance, as well as its can not be identified. These parameters are present in the force-time curve of a maximal voluntary contraction, consisting of i) phase of force generation that involves a rapid development of the force, ii) peak force, iii) force maintenance phase, and iv) declining phase, involving constant rate of force reduction [9, 23].

In this study, we observed significant differences in the time variable, where the groups treated with statin, exercised or not, presented a longer time to reach the maximum strength when compared to the group exercised only. The correlation results reinforce the influence of drug exposure, not exercise. It was also verified that the time values were significantly related to the values of loss of strength, indicating that the lower loss presented by the treated and exercised group is due to obtaining the maximum values of strength near the end of the test. It should be noted, however, that the strength loss of the treated group was not statistically different from that only exercised, indicating that the exercise may have contributed to greater strength maintenance in subjects treated with statin, exerting a positive effect on the strength quality of these individuals.

Otruba, Kanovsky [24] found that although treatment with simvastatin (20mg) for 24 months did not lead to clinical changes in the neurological examination of 42 hyperlipidemic patients, there were changes in the results of electromyography (EMG), characterized by the reduction of fibular nerve conduction velocity, as well as prolongation of the latency of the fibular and tibial nerves, indicating that, despite being clinically silent, the neuronal disturbances caused by the statin are clearly demonstrable.

Thus, the longer time required to reach the peak force values observed in subjects treated with statins is a response compatible with the reduction of motor neurons [25], nerve impulse delay, and with atrophy and / or reduction in the amount of type 2 fibers [24, 26] checked for neuropathy. In these cases, considering that the most expressive differences in the strength profile between the individuals exposed or not to the drug were related to the longer time to reach maximum values of muscle strength, perhaps the design of specific protocols of force evaluation may contribute to the monitoring of muscle changes during this treatment.

**CONCLUSIONS**

The results showed that the continued use of statins did not present significant impairment of the maximum values of muscle strength, however, they directly interfered in the values
of the manual grip force-time curve, which may contribute to the worsening of the quality of life of the individuals affected. However, physical exercise proved to be an important ally of statin therapy, attenuating the adverse effects of the drug on skeletal muscle.

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OBSERVAÇÃO: Os autores declaram não existir conflitos de interesse de qualquer natureza.