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# Adding exercise training to rosuvastatin treatment: influence on serum lipids and biomarkers of muscle and liver damage

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**Abstract**

Statin treatment and exercise training can improve lipid profile when administered separately. The efficacy of exercise and statin treatment combined, and its impact on myalgia and serum creatine kinase (CK) have not been completely addressed. The purpose of this study was to determine the effect of statin treatment and the addition of exercise training on lipid profile, including oxidized low-density lipoprotein (oxLDL), and levels of CK and alanine transaminase. Thirty-one hypercholesterolemic and physically inactive subjects were randomly assigned to rosuvastatin (R) or rosuvastatin/exercise (RE) group. A third group of physically active hypercholesterolemic subjects served as an active control group (AC). The R and RE groups received rosuvastatin treatment (10 mg/d) for 20 weeks. From week 10 to week 20, the RE group also participated in a combined endurance and resistive exercise training program (3 d/wk). Lipid profile was determined for all subjects at week 0 (Pre), week 10 (Mid), and week 20 (Post). The CK and alanine transaminase levels were measured at the same time points in the RE and R groups and 48 hours after the first and fifth exercise bout in the RE group. Each RE subject was formally queried about muscle fatigue, soreness, and stiffness before each training session. Total, LDL, and oxLDL cholesterol was lower in the RE and R groups at Mid and Post time points when compared with Pre. Oxidized LDL was lower in the RE group compared with the R group at the Post time point. When treatment groups (R and RE) were combined, high-density lipoprotein levels were increased and triglycerides decreased across time. Creatine kinase increased in the RE group 48 hours after the first exercise bout, but returned to baseline levels 48 hours after the fifth exercise bout. Rosuvastatin treatment decreased total, LDL, and oxLDL cholesterol. The addition of an exercise training program resulted in a further decrease in oxLDL. There was no abnormal sustained increase in CK or reports of myalgia after the addition of exercise training to rosuvastatin treatment.


## 1. Introduction

Hypercholesterolemia is recognized as being atherogenic and a significant independent risk factor for the future development of cardiovascular disease (CVD) [1,2]. The link between serum lipid levels and CVD risk has been clearly emphasized in large-scale clinical trials wherein a reduction in CVD risk was observed when total and low-density lipoprotein (LDL) cholesterol was reduced by pharmacologic intervention [3-6].

Hydroxymethylglutaryl–coenzyme A reductase inhibitors or statin drugs are the most effective pharmacologic intervention for hypercholesterolemia [7]. Numerous epidemiologic studies have been completed in which the safety and efficacy of statin drugs for reducing cardiovascular morbidity and mortality were demonstrated [8-10]. Rosuvastatin's ability to lower LDL cholesterol has been demonstrated to be greater than that of other statins [11,12].

Exercise or regular physical activity also prevents the development of CVD and related mortality [13-15]. The reduction in CVD elicited by exercise training is at least partially mediated by favorable changes in circulating lipoproteins [16,17]. A number of meta-analysis studies have been conducted, the results of which indicate that regular exercise can lower LDL and total cholesterol and

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increase high-density lipoprotein (HDL) cholesterol [18-20]. Furthermore, acute exercise causes an increase in oxidative stress, resulting in a subsequent transient increase in the oxidizability of LDL; however, regular exercise has been shown to lower the resting blood levels of oxidized LDL (oxLDL) [21,22].

Statin use is considered safe; but cases of myalgia, myositis [23,24], and more rarely rhabdomyolysis [25,26] have been reported as adverse effects. Although statin-induced rhabdomyolysis is rare, muscle pain, weakness, and subclinical indicators of muscle damage are more commonly reported [27]. Novel exercise often results in muscle damage and subsequent increases in circulating creatine kinase (CK) [28]. Therefore, the possibility exists that statin treatment and exercise training combined could increase the severity of muscle damage and increase circulating CK levels. Lovastatin treatment exacerbated the CK increases induced by an acute bout of exercise [29,30]. There have also been case study reports of statin treatment reducing exercise tolerance [31,32].

The purpose of this study was to determine whether the addition of an exercise training program to rosuvastatin treatment would result in an additional improvement in lipid profile, including oxLDL levels, in hypercholesterolemic patients. A secondary purpose was to examine possible exercise training–induced incidence of muscle fatigue and soreness as well as serum CK and alanine transaminase (ALT) levels as indicators of muscle damage and liver toxicity.

## 2. Methods

### 2.1. Study design

Thirty-one hypercholesterolemic (total, >200 mg/dL; LDL, >130 mg/dL) and physically inactive male (40-65 years old) and female (45-65 years old and postmenopausal) subjects were randomly divided into 2 groups: a rosuvastatin/exercise group (RE; 8 women, 7 men) and a rosuvastatin group (R; 8 women, 8 men). Subjects in the R and RE groups received a daily dose of rosuvastatin calcium (10 mg) for 20 weeks. From week 10 to 20, RE subjects also completed an exercise training program. Fifteen physically active and hypercholesterolemic (total, >200 mg/dL; LDL, <160 mg/dL) subjects were recruited for the active control group (AC; 8 women, 7 men). The AC group received no treatment because they did not have a CVD risk level that required drug treatment as determined by the Adult Treatment Program III guidelines [33].

The RE and R subjects required a signed consent letter from their personal physician and a prescription for rosuvastatin calcium (10 mg/d) before starting the study. The prescription for rosuvastatin calcium was filled at Purdue University pharmacy. The study was approved by the Biomedical Institutional Review Board at Purdue University (protocol 0505002668).

### 2.2. Screening

One week before the baseline trial day, potential subjects reported to the laboratory in a fasted state for screening. Potential subjects read and signed an Institutional Review Board–approved informed consent document and completed a medical history questionnaire. Potential subjects were disqualified if they reported previous myocardial infarction or stroke, a history of liver or kidney disease, musculoskeletal or orthopedic limitations, signs of acute illness, hypothyroidism, diabetes mellitus, or renal insufficiency. Furthermore, potential subjects being treated with cyclosporine, warfarin, gemfibrozil, other lipid-lowering drugs, or any medications known to interact with statin drugs were excluded from the study.

After 20 minutes of seated rest, blood was drawn by venipuncture from an antecubital vein using a sterile, single-use needle and evacuated SST tubes (Becton-Dickinson, Franklin Lakes, NJ). Aliquots of serum were stored at −80°C until further analysis. Total cholesterol, HDL cholesterol, and triglycerides were determined for each subject. Percentage body fat was determined by a 3-site skinfold method [34]. All participants had a body mass index (BMI) less than 35 kg/m$^2$.

A physical activity questionnaire [35] and a modified Balke submaximal treadmill test, to estimate maximum oxygen consumption ($Vo_{2max}$) [34], were used to assess physical activity levels for group assignments. To be assigned to the AC group, subjects were required to be exercising at least 3 days per week for the previous 6 months and to have a “good” to “superior” estimated $Vo_{2max}$ (women, >28 mL/[kg min]; men, >35 mL/[kg min]). For the R and RE groups, subjects were required to have had little or no regular exercise over the past 6 months and a “fair” to “very poor” $Vo_{2max}$ (women, <25 mL/[kg min]; men, <32 mL/[kg min]).

Physically inactive subjects with total cholesterol higher than 200 mg/dL and LDL higher than 130 mg/dL were assigned to the R and RE groups. Physically active subjects with total cholesterol higher than 200 mg/dL, LDL cholesterol less than 160 mg/dL, and a CVD risk level that did not require drug treatment of hypercholesterolemia were enrolled into the AC group. Subjects in the AC group were asked to maintain their physically active lifestyle and record daily exercise in a log.

A total of 49 subjects were recruited, and 46 subjects completed the study. Three subjects dropped out of the study for personal reasons (2 AC, male; 1 RE, male).

### 2.3. Acclimation and exercise training

After 10 weeks of rosuvastatin treatment, subjects in the RE group completed 3 acclimation sessions on nonconsecutive days before beginning their exercise training program. On the first acclimation day, subjects were taught the correct lifting technique for performing the following exercises: leg press, leg extension, leg curl, chest press, lat pull-down,

seated row, leg adduction, and leg abduction (Keiser, Fresno, CA). A modified Balke submaximal treadmill test to estimate $V_{O_{2max}}$ was also conducted [34]. On the second acclimation day, 8-repetition maximum (RM) was determined for each of the strength exercises. Finally, on the third acclimation, 1 RM was determined for the chest press, leg press, and leg curl.

After acclimation, RE subjects completed approximately 10 weeks (3 d/wk) of combined endurance and resistive exercise training. The endurance training portion consisted of 20 minutes of walking on the treadmill at 60% to 70% of heart rate reserve. After treadmill walking, RE subjects completed a series of 6 stretches and performed 2 sets of 8 resistance exercises (70%-80% of 1 RM). The RE subjects were reassessed for 8 RM, 1 RM, and estimated $V_{O_{2max}}$ at the end of the training period (30 sessions).

### 2.4. Trial day procedure

Blood samples were collected as previously described at baseline and after 10 and 20 weeks of the treatment or control periods. On the day before each blood draw, subjects were required to follow a suggested 1-day eucaloric diet, which was designed to contain approximately 50% carbohydrate, 35% fat, and 15% protein. Subjects reported to the laboratory on the following morning in a fasted state and 72 hours removed from the last bout of exercise.

### 2.5. CK and ALT assay

Serum levels of CK and ALT were measured in R and RE at week 0; 5 and 10 weeks after the start of rosuvastatin treatment; and, in the RE group only, 48 hours after the first and fifth exercise bout. Creatine kinase and ALT were quantified using a 1-step standard kinetic (ALT) and end point (CK) colorimetric assay using Infinity reagents (Thermo Electron, Waltham, MA). Normal and abnormal controls were run with each batch of samples tested. The intraassay coefficients of variation for the ALT and CK assays were 0.49% and 5.70%, respectively.

Subjects in the RE group were also formally screened for muscle tenderness, stiffness, soreness, weakness, constipation, abdominal pain, or nausea using a questionnaire administered before the start of each training session. Subjects with abnormal elevations in CK or ALT or with other symptoms were referred to their physician for permission to continue in the study.

### 2.6. Measurement of serum cholesterol and triglyceride

Lipid profile was determined for all subjects at week 0 (Pre), week 10 (Mid), and week 20 (Post). Total and HDL cholesterol was quantified by a standard colorimetric assay (Thermo Electron). Triglycerides were determined by a standard end point colorimetric assay (Thermo Electron). Low-density lipoprotein cholesterol was estimated using the Friedewald equation [36]. The inter- and intraassay coefficients of variation for the cholesterol assay were 6.35% and 3.16%, respectively. The inter- and intraassay coefficients of variation for the triglyceride assay were 8.6% and 3.3%, respectively.

### 2.7. Serum oxLDL

Serum oxLDL was measured by a commercially available solid-phase 2-site enzyme immunoassay (ALPCO Diagnostics, Salem, NH). The specific form of oxLDL detected by this assay is malondialdehyde-modified LDL. The assay was carried out according to the manufacturer's instructions. The inter- and intraassay coefficients of variation for the oxLDL assay were 8.8% and 4.7%, respectively.

### 2.8. Statistical analysis

All data are reported as mean ± standard error. All statistical analyses were performed using Base SAS (Cary, NC) Version 9.0. Before statistical analysis, all data were tested for the assumptions of normality, equality of variance, and independence. Analysis of variance (group × time) was used to determined significant time and group differences in all variables. Tukey post hoc test was used to determine if comparisons were significant. The level of statistical significance was set at $P$ less than .05.

## 3. Results

### 3.1. Subject descriptive data

There were no significant changes in weight, BMI, or percentage body fat in any group with the intervention. The R group had a slightly but significantly higher body mass than the RE group, but the BMI and body fat levels were not significantly different between these groups. There was a significant group effect, such that AC had lower body mass, BMI, and percentage body fat than the R and RE groups (Table 1).

### 3.2. Aerobic fitness and strength

The AC group had a significantly higher $V_{O_{2max}}$ compared with the RE and R groups. Maximum oxygen consumption increased significantly in the RE group after exercise training (29% ± 6%) (Table 1). Muscular strength increased significantly for all exercises (8 RM range, 30% ± 4% to 57% ± 10%; 1 RM range, 16% ± 3% to 20% ± 17%) in the RE group. The average number of training sessions completed by the RE group was 29 (range, 26-30 sessions).

### 3.3. Serum cholesterol and triglyceride

Total and LDL cholesterol was lower in the AC group compared with the R and RE groups at Pre. Total and LDL cholesterol for the R and RE groups was also lower at the Mid and Post time point compared with Pre. There was no significant effect for exercise training; however, total and LDL cholesterol tended to be lower in the RE group

Table 1
Descriptive data for AC, R, and RE groups Pre and Post intervention or control period

| Group | n | Age (y) | Height (cm) | Body mass (kg) | | BMI (kg/m$^2$) | | % Body fat | | $Vo_{2max}$ (mL/[kg min]) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| AC | 8 F, 7 M | 51.60 ± 1.13 | 171.88 ± 2.59 | 73.57 ± 3.70* | 74.56 ± 3.65* | 23.4 ± 0.78* | 24.83 ± 0.78* | 23.39 ± 1.88* | 25.26 ± 2.05* | 41.05 ± 1.66† | 38.7 ± 1.73† |
| R | 8 F, 8 M | 52.06 ± 1.46 | 170.43 ± 3.38 | 84.24 ± 5.17‡ | 85.68 ± 6.17‡ | 28.41 ± 1.01 | 28.11 ± 0.95 | 31.27 ± 1.83 | 29.57 ± 2.03 | 27.07 ± 1.18 | 28.03 ± 1.20 |
| RE | 8 F, 7 M | 51.6 ± 1.20 | 171.2 ± 2.00 | 80.76 ± 4.85 | 81.25 ± 4.75 | 27.12 ± 1.07 | 27.97 ± 1.16 | 30.00 ± 1.92 | 30.06 ± 1.96 | 27.00 ± 1.09 | 37.48 ± 2.46§ |

F indicates female; M, male.

* Group effect (average of Pre and Post); AC was significantly lower than R ($P < .0001$) and RE ($P < .02$).

† Group effect; $Vo_{2max}$ for the AC group was higher than that for the R and RE groups ($P < .0001$).

‡ Group effect; R was significantly higher than RE ($P < .005$).

§ $Vo_{2max}$ for the RE group was higher at the Post time point when compared with Pre ($P < .0001$).

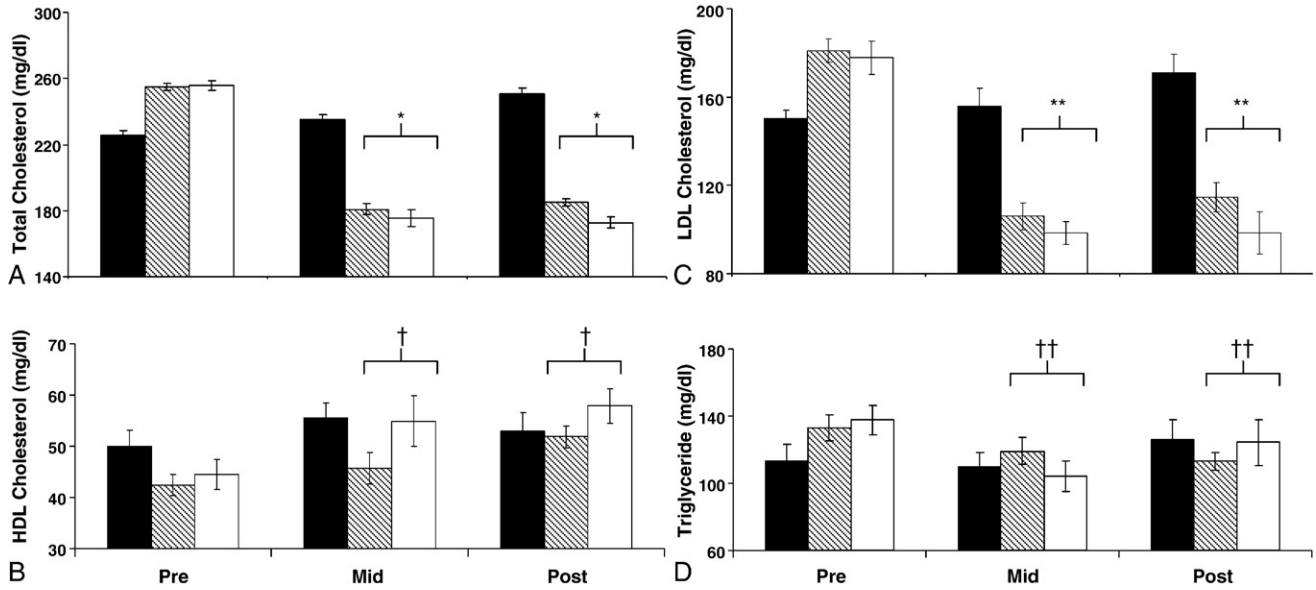


Fig. 1. Lipid profile in the AC (black), R (hatched), and RE (white) groups. A, *Total cholesterol was lower in the R and RE groups compared with Pre ($P < .0001$), and compared with the AC group at Mid and Post ($P < .0001$). B, †High-density lipoprotein cholesterol was higher in the intervention groups combined at Mid ($P < .05$) and Post ($P < .005$) compared with Pre. C, **Low-density lipoprotein cholesterol was lower in the R and RE groups compared with Pre ($P < .0001$), and compared with the AC group at Mid and Post ($P < .0001$). D, ††Triglycerides were lower in the intervention groups combined compared with Pre ($P < .005$).

compared with the R group at Post. There was a time effect for HDL cholesterol, such that the value for the R and RE groups combined was higher at Mid and Post time points compared with Pre. There was a time effect for serum triglyceride levels, such that the value for the R and RE groups combined was lower at Mid and Post time points compared with Pre (Fig. 1).

### 3.4. Serum oxLDL cholesterol

There was a significant interaction effect for oxLDL. In the R and RE groups, oxLDL was significantly lower at the Mid and Post time points compared with Pre. There was also a significant difference between the RE and R groups at the Post time point, such that RE had significantly lower oxLDL than the R group, suggesting an exercise training effect (Fig. 2). It was found that oxLDL cholesterol and LDL cholesterol were strongly correlated ($r = 0.672$, $P = .0001$);

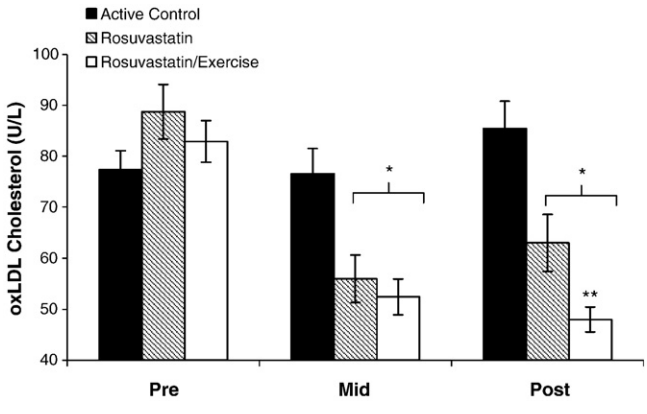


Fig. 2. Oxidized LDL cholesterol levels. *Oxidized LDL was lower in the R and RE groups compared with Pre ($P < .0001$), and compared with the AC group at Mid and Post ($P < .0001$). **Oxidized LDL was lower in the RE group compared with the R group at the Post time point ($P < .05$).

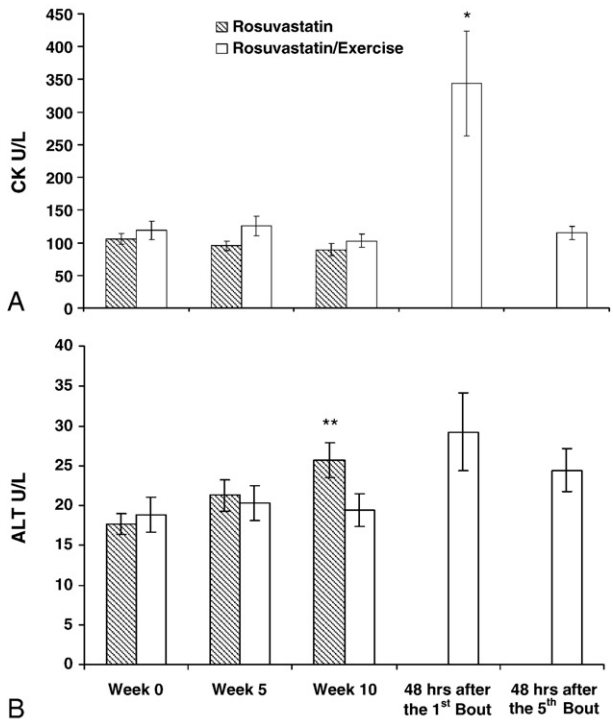


Fig. 3. Creatine kinase and ALT levels. A, *Serum CK was higher 48 hours after the first exercise bout ($P < .0001$). B, **Serum ALT was higher in the R group at week 10 compared with week 0 ($P < .05$).

however, the oxLDL/LDL cholesterol ratio did not change significantly with the intervention and was not different between groups.

### 3.5. Serum CK, ALT, and symptoms of myalgia

A significant increase in CK was observed in the RE group 48 hours after the first exercise training bout when compared with the Pre time point (343 v 119 U/L) However, 48 hours after the fifth exercise bout, CK levels had returned to baseline levels. Furthermore, the maximum increase in CK observed in RE subjects was 1076 U/L; and none experienced CK levels greater than 10 times the upper limit of normal. Serum ALT increased in the R group at the Mid time point compared with Pre (Fig. 3), but remained in the normal physiologic range.

Reports of muscle soreness, tiredness, and fatigue from RE subjects were infrequent and were not any greater than what would be expected from subjects in an exercise training program. Each of 11 subjects reported muscle soreness, tiredness, or fatigue an average of 3 times (range, 1-7 reports) over the 10-week training program. There was no correlation between increased level of CK in RE subjects and reports of muscle stiffness, soreness, or fatigue ($r = 0.17$, $P > .05$). In addition, when individual subject's CK levels over the course of the intervention were averaged and grouped by tertiles, subjects in the highest CK tertile did not report a higher occurrence of muscle stiffness, soreness, or fatigue (data not shown). Finally, no training sessions were missed because of muscle stiffness, soreness, or fatigue.

## 4. Discussion

This study was conducted to determine whether the addition of an exercise training program to rosuvastatin treatment would influence serum cholesterol, triglyceride, and oxLDL levels in hypercholesterolemic patients. We also sought to determine the incidence of rosuvastatin/exercise-induced myalgia and monitored serum CK and ALT levels as indicators of muscle and liver damage, respectively.

The changes in serum lipid levels with 10 mg/d of rosuvastatin were comparable with those observed in a number of previously published studies [12,37,38]. The decrease observed for total cholesterol, LDL cholesterol, and triglycerides in the R and RE groups from Pre to Mid is consistent with a previous report in which hypercholesterolemic patients were treated for 6 weeks with rosuvastatin (10 mg/d) [39].

We hypothesized that exercise would elicit an additional lowering of total and LDL cholesterol. It was previously suggested that exercise training can lower total cholesterol, LDL cholesterol, and triglycerides, and increase HDL cholesterol [20]. However, more recent reports suggest that effects on LDL and total cholesterol are small and can be inconsistent [18,19]. The addition of exercise to rosuvastatin treatment did not significantly alter blood lipids compared with rosuvastatin treatment alone. However, there was a tendency for the RE group to have lower total and LDL cholesterol and higher HDL cholesterol compared with the R group at the Post time point, albeit these differences were not statistically significance.

The additive effect of exercise training and statin therapy on lipid profile was previously examined by Wittke (1999) [40]. It was found that an exercise-only intervention elicited favorable changes to lipid profile (triglyceride, −24.7%; HDL, +19.3%; LDL, −12.8%). A second group who had already been treated with fluvastatin for at least 3 months before starting the same exercise program had a smaller yet significant improvement in lipid profile after the addition of exercise training (triglyceride, −12.88%; HDL, +13.81%; LDL, −8.7%) [40]. The results of the Wittke (1999) study suggest that adding exercise training to statin therapy has an additive effect on improving lipid profile, and are in contrast to the results generated in the present study. A partial explanation for the contrasting results may relate to the high baseline lipid levels of subjects in the Wittke (1999) study, in which the baseline serum LDL cholesterol was 158 mg/dL for the pretreatment group. In the present study, the LDL level of subjects in the RE group before starting the exercise training program was 98.4 mg/dL, suggesting that total and LDL cholesterol concentrations were already at their nadir by the Mid time point in the present study, making it difficult for exercise to elicit an additive effect. Furthermore, Olsson et al [39] found that approximately 90% of rosuvastatin-induced reduction in LDL cholesterol occurred within the first 2 weeks of treatment.

Oxidized LDL is reported to be positively correlated with CVD and acute cardiac events [41,42] and is also involved in the pathophysiology of atherosclerotic plaque development [43,44]. Enzyme-linked immunosorbent assay kits to measure serum levels of oxLDL have recently become commercially available [45]. Before this, measurements of the oxidizability of LDL and serum antibodies against LDL were used as indices of oxLDL concentration. Statin treatment reduced markers of oxidative stress, autoantibodies against modified lipoprotein, and LDL oxidation as measured using diene conjugation [46,47]. Furthermore, both Ndrepepa et al [41] and van Tits et al [48] reported the ability of statin drugs to lower the concentration of oxLDL. Rosuvastatin (10 mg/[kg d]) was previously reported to reduce oxLDL buildup in the aortic plaque of obese dyslipidemic mice [49] and to reduce circulating levels of antibodies against modified LDL [46]. We observed a decrease in oxLDL in the R (−39% ± 2%) and RE (−34% ± 7%) groups from Pre to Mid. The magnitude of decrease is consistent with previous reports for other statin drugs [50,51]. The RE group had lower Post levels of oxLDL than the R group, indicating an additive effect of exercise. Exercise was previously shown to reduce oxLDL or proxy measures of oxLDL [21,22]. This is significant because statin treatment is prescribed along with

recommendations for lifestyle changes, such as increasing physical activity [33]. However, the additive effects of exercise and statin treatment have not been investigated thoroughly; and, to our knowledge, this is the first report of an additive decrease in oxLDL when exercise training was combined with statin treatment.

In a recent report, van der Zwan et al [52] describes how the ratio of oxLDL to LDL cholesterol and apolipoprotein B-100 may prove more valuable as a clinical indicator of atherosclerosis than oxLDL alone. Van der Zwan et al found that the oxLDL/LDL cholesterol ratio and the oxLDL to apolipoprotein B-100 ratio were more negatively correlated with flow-mediated dilation of the brachial artery than oxLDL alone. In the present study, we found that oxLDL cholesterol and LDL cholesterol were strongly correlated. Furthermore, although oxLDL was lower in R compared with RE at the Post time point, the oxLDL/LDL cholesterol ratio was not significantly different between groups or over time. It is possible that nonsignificant variance in LDL cholesterol levels between groups and the fact that LDL cholesterol and oxLDL are not absolutely correlated ($r = 0.672$) may explain why we did not observe a significant difference in oxLDL/LDL cholesterol ratio between R and RE at the Post time point, whereas oxLDL was significantly different.

Creatine kinase increased in the RE group 48 hours after the first bout of exercise when compared with baseline, as would be expected after a novel bout of exercise. Forty-eight hours after the fifth bout, CK levels had returned to baseline. Reported muscle soreness, tiredness, and fatigue were determined by administering a questionnaire before each training session. There were no significant increases in muscle soreness, tiredness, and fatigue other than what would be expected from such a training program. Eleven subjects reported soreness and stiffness, and these complaints were transient and not apparent within 2 days/weeks of the original complaint. There were also no correlations between increased level of CK in RE subjects and the incidence of muscle stiffness, soreness, or fatigue ($P > .05$, $r = 0.17$). When the average CK level over the course of the intervention for each subject was grouped by tertiles, subjects in the highest CK tertile did not report a significantly higher incidence of muscle stiffness, soreness, or fatigue (data not shown).

A combination of exercise and statin treatment was reported to induce an additive increase in circulating CK levels in 2 previous studies [29,30]. However, these studies used different exercise interventions than were used in the present study. The intervention of Thompson et al [30] included acute bouts of exercise, specifically intended to induce muscle damage. For example, CK was measured in nontrained subjects before and after 45 minutes of downhill treadmill walking (−15% grade) at 65% of their predetermined maximum heart rate. The exercise protocol was implemented before and after 5 weeks of lovastatin treatment [30]. Creatine kinase levels were 62% and 77% higher in the lovastatin group 24 and 48 hours after treadmill exercise when compared with the placebo group. The second Thompson et al [29] (1991) study observed no group differences in CK levels between lovastatin and placebo. However, 2 individual subjects had significantly increased CK after the exercise test during lovastatin administration [29]. The results from these studies suggest that statin pretreatment may exacerbate CK elevations after an acute bout of muscle-damaging exercise. In contrast, our findings suggest that a moderate and progressive endurance and resistance training program was well tolerated by older men and women taking rosuvastatin. It was also reported that, in a group of elite athletes with familial hypercholesterolemia, only 20% tolerated statin treatment without adverse effects [32]. It is possible that the higher level of training of these athletes might contribute to the increased incidence of adverse effects.

Minor increases in ALT after statin treatment have been previously reported [53]. For example, 2.6% and 5.0% of patients receiving lovastatin doses of 20 and 80 mg/d, respectively, were observed to have serum ALT levels that were 3 times greater than those at baseline. In the present study, we observed an increase in ALT in the R group; however, the increase was less than 1 times baseline levels and was not likely to be clinically relevant. The ALT mean values were in the reference range for all groups at all time points.

A limitation associated with the present study was the lack of an exercise training–only intervention, making it difficult to assess the effects of exercise alone. However, the aim of the present study was to examine the effects of exercise training in patients already taking rosuvastatin. This design allowed us to assess potential additive effects of exercise and to determine that subjects on rosuvastatin responded favorably to supervised, strenuous exercise.

In conclusion, rosuvastatin treatment effectively lowered total, LDL, and oxLDL cholesterol, without a persistent increase in CK or reports of myalgia in hypercholesterolemic patients. The addition of an exercise training program decreased oxLDL in the RE group when compared with the R group. The results from the present study suggest that a progressive and moderate exercise program and statin treatment may provide additive benefit to hypercholesterolemic patients without persistent additive increases in CK and muscle myalgia.

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