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Statins and Dietary and Serum Cholesterol Are Associated With Increased Lean Mass Following Resistance Training

Steven E. Riechman,[1–3] Ryan D. Andrews,[3,4] David A. MacLean,[3,5] and Simon Sheather[6]

Departments of [1]Health and Kinesiology, Texas A&M University, College Station, Texas.
[2]University of Pittsburgh, Human Genetics, Pennsylvania.
[3]Kent State University, Ohio.
[4]The Johns Hopkins Weight Management Center, Baltimore, Maryland.
[5]Division of Medical Sciences, Northern Ontario School of Medicine, Sudbury & Thunder Bay, Ontario, Canada.
[6]Department of Statistics, Texas A&M University, College Station, Texas.

Background. Age-related muscle loss (sarcopenia) is a prevalent condition associated with disability and mortality. Exercise and optimal nutrition are interventions to prevent and treat sarcopenia, yet little is known, outside of protein, of the effect of common nutrition recommendations and medication use on exercise-related muscle gain.

Methods. Forty-nine community-dwelling, 60- to 69-year-old men and women completed 2 weeks of nutrition education (American Dietetic Association recommendations) followed by 12 weeks of high intensity resistance exercise training (RET) with postexercise protein supplementation and 3×/wk dietary logs.

Results. We observed a dose-response relationship between dietary cholesterol (from food logs) and gains in lean mass that was not affected by variability in protein intake. Serum cholesterol and the serum cholesterol lowering agent statin were also independently associated with greater increases in lean mass. Dietary cholesterol was not associated with serum cholesterol or the significant reduction in blood pressure observed, but trends were observed for altered plasma C-reactive protein.

Conclusion. These data suggest that dietary and serum cholesterol contribute to the skeletal muscles' response to RET in this generally healthy older population and that some statins may improve this response.

SKELETAL muscle is lost at a rate of approximately 5% per decade after the age of 40 (1). Muscle mass is the major determinant of physical strength, thus the loss of lean mass is thought to be a major contributor to functional decline and disability (2,3). After the age of 60, the prevalence of moderate and severe sarcopenia has been estimated at 53% and 11% in men and 22% and 9% in women, respectively (2,3). Sarcopenia is associated with a greater risk of disability and costs $18.5 billion or 1.5% of the total health care expenditure in the United States (2,3). These costs will accelerate as the population older than 65 years grows from 13% (1997) to 17% in 2020 and 21% by 2040 (4).

Exercise and nutrition are modifiable risk factors for sarcopenia (5,6) as well as for other major chronic diseases of aging including cardiovascular disease (CVD), diabetes, and obesity (7,8). Endurance-type physical activity, calorie restriction, and reduction in saturated fat and cholesterol are emphasized for reducing the risk of CVD, diabetes, and obesity. These interventions are effective at inducing weight loss, lowering serum lipids, improving endurance capacity, and lowering the risk of disease (7,8). However, to prevent muscle loss, resistance-type physical activity along with increased protein is recommended (5,6). In order to study these differences in recommended nutrition and exercise interventions, we evaluated the effect of dietary and serum lipids, and lipid-lowering drugs (statins) on an intervention designed to increase lean mass. Statin use and other lipid-lowering strategies are associated with many skeletal muscle pathologies including rhabdomyolysis, myalgia, myositis, muscle weakness, and cramps (9). Therefore, we hypothesized that lower dietary cholesterol intake, serum cholesterol, and statin use would be associated with reduced skeletal muscle responses to the intervention.

Methods

Participants

This study was approved by the Kent State University Institutional Review Board. After all procedures were explained, participants provided written informed consent. Enrolled participants included men ($N = 25$) and women ($N = 30$) aged 60–69 years old who were generally healthy, nonsmoking, and able to perform exercise testing and training. Participants were excluded if a medical history or physical examination by a nurse practitioner revealed blood pressure > 160/100 mmHg, cardiac arrhythmias, cancer, hernia, aortic aneurysm, kidney disease, or lung disease. Also excluded were those individuals who engaged in 1 hour or more of resistance exercise training (RET) per week in the past year. This study still included several participants who took medications common for this age group. These medications included hormone replacement therapy ($N = 7$), antiosteoporotics ($N = 4$), thyroid medications ($N = 5$),

antihypertensives ($N = 9$), antidepressants ($N = 3$), prostate medications ($N = 3$), and gastric reflux medications ($N = 7$). A total of 17 participants were taking one medication, and six participants were taking more than one medication. Six individuals were not included in analyses due to poor attendance ($N = 1$, stopped attending), incomplete dietary logs ($N = 1$), blood pressure > 160/100 mmHg ($N = 1$), or incomplete blood samples ($N = 3$).

Orientation/Education

Prior to the intervention, participants attended six orientation/education sessions over 2 weeks that included 1 hour of RET at 40%–50% of maximal effort and 30 minutes of nutritional education. Conducting RET orientation may reduce the likelihood of injury and induce rapid motor learning, thus assisting standardization of maximal strength measures (10). Diet education emphasized consuming > 1.0 g/kg protein; isocaloric intake; macronutrient ratio of 50% carbohydrate, 30% fat, 20% protein; saturated fat intake < 10% total calories; cholesterol intake < 300 mg/d; and 25–30 g fiber/d (based on American Dietetic Association recommendations) (11). These sessions also included training and practice on completing dietary logs.

Testing

Following the education/orientation sessions and at the completion of 12 weeks of RET, maximal strength (1 RM), body composition (dual energy x-ray absorptiometry, DEXA), resting energy expenditure, blood pressure (DINAMAP 400 automated NIBP; GE Medical, Piscataway, NJ), plasma high sensitivity C-reactive protein (hsCRP), and fasting lipid profile were measured. Strength (1 RM) was measured on all exercises included in the RET by progressive increases in weight until execution was not successful (12). Whole body and regional body composition scans were conducted using a Hologic 4500 Elite DEXA (Bedford, MA). Resting metabolic rate and duplicate blood pressures (coefficient of variation [CV] % < 3%) were measured in the morning after an overnight fast and after 30 minutes of resting supine within 1 week of starting the intervention and within 3 days of completing the intervention. Oxygen consumption measures were collected using Parvo-Medics TrueMax 2400 Metabolic Measurement System (Sandy, UT) until stable (CV < 10%) figures were obtained (13). Twelve hours after a standardized meal (50% carbohydrate, 30% fat, 20% protein), fasting blood samples were collected from an antecubital vein. Lipids were measured by using standard methods at the Heinz Nutrition Laboratory at the University of Pittsburgh (14). Enzyme-linked immunosorbent assay (ELISA; Life Diagnostics, Inc., West Chester, PA) was used to measure hsCRP. Inter- and intra-assay CV was < 5% for all assays. CRP data were log transformed for statistical analysis although unadjusted means are presented for the purpose of comparison to other investigations.

Intervention

Three days a week for 12 weeks, participants performed RET at the Kent State Exercise Laboratory. RET included 10 minutes of cycle ergometry warm-up, 5 minutes of stretching, and three sets of 8–12 repetitions of eight resistance exercises with weights set at 75% of 1 RM. Exercises included chest and leg press, knee extension and flexion, triceps extension and biceps curl, calf raise, and lat pulldown (Cybex; Cybex International, Inc., Medway, MA). Participants were instructed to perform as many repetitions as possible up to 12 repetitions. When a participant achieved three sets of 12 repetitions of an exercise, the weight was increased. At each session, participants submitted a 24-hour dietary log and consumed 0.4 g protein/kg lean mass (Boost HP; Novartis, Fremont, MI) immediately after exercise. Dietary protein recommendations and postexercise protein supplements were intended to minimize variability of muscle gains due to protein intake variability (15,16). Participants who missed exercise sessions attended make-up sessions. If it was necessary to conduct make-up sessions on consecutive days, participants performed five sets of all upper body exercises on the first day and five sets of all lower body exercises on the second day. No participant did more than five make-up sessions, and everyone did at least one.

Statistical Analyses

All analyses were conducted using SPSS statistical software (version 11.0; SPSS Inc., Chicago, IL) and the SIMEX package in R (http://www.r-project.org/). The thirty-six, 24-hour dietary logs were entered into Nutribase V Clinical software (Cybersoft, Inc., Phoenix, AZ) to generate the means of all macro- and micronutrients. Means of the first six and last six records were compared by paired t test to confirm consistency in dietary patterns throughout the trial. Mean nutrient values of all 36 records, adjusted for an individual's baseline lean mass, were evaluated by Pearson's correlations for association to RET responses. Separate analyses were conducted evaluating the effect of adiposity and dietary adjustments based on total mass. We are presently reporting adjustments to only lean mass for the following reasons: Adjustments to lean mass lead to stronger associations, adiposity was not associated to outcome variables, and lean tissue is the most metabolically active and therefore sensitive to nutrient fluctuations. Mean changes in relative RET responses were similar between men and women; therefore, data were pooled for analyses of relative changes. Strength changes were reported as the percent increase from baseline of the sum of chest press and leg press. RET responses for lean mass, serum lipids plasma, hsCRP, blood pressure, and heart rates were analyzed by one- and two-way analyses of variance (ANOVAs) with repeated measures. For blood markers of cardiovascular risk (blood pressure, lipids, and hsCRP), two-way ANOVAs (statins, dietary cholesterol categories) was used covarying gender, adiposity, and medications. Dietary cholesterol adjusted for lean mass was also submitted to linear regression along with total serum cholesterol and low-density lipoprotein (LDL) cholesterol, statin use (none [$n = 37$)], atorvastatin/simvastatin group [$n = 8$] and pravastatin/lovastatin group [$n = 4$]), potential covariates (body fat and gender), and interactions to determine the independent associations of these factors on muscle responses with RET. Analyses were also conducted allowing for measurement error. The regression models allowing for measurement errors in dietary cholesterol, serum cholesterol,

Table 1. Participant Characteristics Before and After Training

	Dietary Cholesterol (mg/kg lean mass/d)							
	2.2–3.5 (N = 7/6)*		3.6–4.4 (N = 6/5)*		4.7–6.9 (N = 5/12)*		7.2–10.3 (N = 5/3)*	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age, y								
Pretraining	64.2	2.4	64.8	4.0	63.6	2.7	62.9	2.3
Height, m								
Pretraining	1.69	0.10	1.72	0.08	1.65	0.09	1.67	0.12
Weight, kg								
Pretraining	82.1	13.7	82.4	18.9	77.4	12.2	79.7	19.4
Posttraining	80.7	14.4	81.4	20.4	77.3	11.9	81.0	19.2
Fat, %								
Pretraining	32.0	8.0	31.6	8.5	35.0	8.8	35.4	6.9
Posttraining	29.9	7.8	28.5	7.5	33.0	9.0	33.6	7.3
Lean mass, kg†								
Pretraining	51.3	12.0	50.6	11.5	45.0	8.5	45.9	13.5
Posttraining	51.4	12.1	51.5	12.5	46.4	13.7	48.4	14.3
BMI, kg · m^{-2}								
Pretraining	28.8	3.4	27.6	4.2	28.4	4.3	28.4	5.3
Posttraining	28.3	3.5	27.1	4.4	28.4	4.3	28.8	5.3
Lean mass index, kg · m^{-2}†								
Pretraining	17.8	2.5	16.9	2.3	16.4	2.1	16.2	2.9
Posttraining	17.8	2.5	17.2	2.6	16.8	4.4	17.0	3.1
Skeletal muscle, kg†								
Pretraining	31.1	7.6	31.6	9.1	28.2	5.5	29.1	11.1
Posttraining	31.6	7.8	33.2	9.7	29.1	5.3	31.1	11.4
Relative SM, kg · m^{-2}†								
Pretraining	10.8	1.6	10.5	2.0	10.3	1.4	10.2	2.9
Posttraining	11.0	1.7	11.0	2.1	10.6	1.4	10.9	2.6

Notes: *Sample size of men/women.
†Sarcopenia criteria, skeletal muscle (SM) = 1.33 · (arm + leg muscle) (1,3).
SD = standard deviation; BMI = body mass index.

and obesity were fit using the SIMEX method [see (17, Chapter 5) for a detailed explanation of the SIMEX method]. The measurement errors in serum cholesterol and obesity were estimated assuming CVs of repeated measurements of 5% and 2%, respectively. Following Carroll and colleagues (17, p. 118), the measurement error in dietary cholesterol was based on half of the variance of the differences between the results for weeks 1–6 and 7–12. Calculations were performed using the SIMEX package in R. Groupings of specific statins were based on preliminary analyses in which differences in exercise responses (change in lean mass) between statin types were observed. Multiple regression analysis was also conducted (excluding all participants taking statins) to examine the possible confounding of cholesterol lowering and altered dietary cholesterol intake in these participants.

Results

Participants' physical characteristics before and after training are presented in Table 1, stratified by dietary cholesterol consumption. Because hypertrophic responses to RET were similar ($p = .55$) between men (+1.3 ± 1.7 kg, 2.1 ± 2.8%) and women (+1.1 ± 1.4 kg, 2.4 ± 2.9%), data were pooled for some analyses. Based on means of the 36 dietary logs, participants consumed 1763 ± 375 kcal and met nutritional recommendations for proportions of macronutrients (51 ± 8% carbohydrate, 32 ± 6% fat, 9 ± 2% saturated fat, 18 ± 3% protein), total protein (0.99 ± 0.22 g/kg), and cholesterol (245 ± 111 mg).

There was not a significant difference in kcal/kg, protein/kg, or cholesterol/kg between quartiles of percent body fat or between genders (data not shown) with the exception of kcal/kg lean mass, which was significantly higher in women (37 vs 33 kcal/kg lean, $p = .04$). No significant differences in intake were observed from the first 2 weeks of training as compared to the last 2 weeks. All participants had average caloric intake that was equal to or greater than that required for energy balance as predicted by resting energy expenditure. Furthermore, adiposity by correlation or quartiles was not significantly associated with lean mass gain with training (data not shown). No associations were observed between medications for hormone replacement therapy, antihypertensives, e.g., and muscle responses with exercise.

The average dietary cholesterol consumption was strongly associated ($r = 0.448$, $p = .001$) with the change in lean mass, which was further strengthened by adjustments for body mass ($r = 0.467$, $p = .001$) and lean mass ($r = 0.512$,

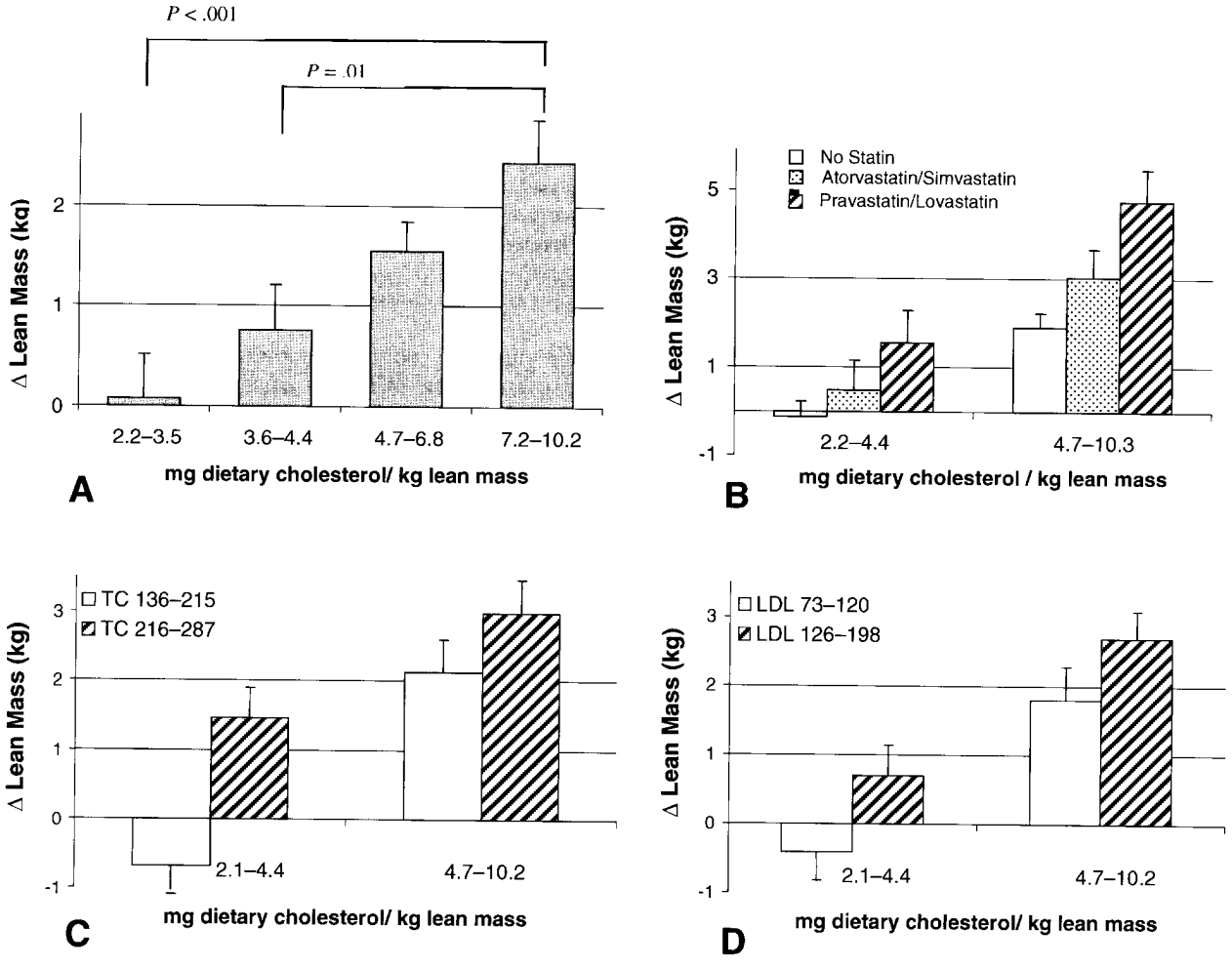

Figure 1. The association of dietary and serum cholesterol and statins with lean mass gains with 12 weeks of high-intensity resistance exercise training in 60- to 69-year-old men and women (estimated marginal means ± standard error). **A**, Effect of dietary cholesterol. $p_{\text{linear trend}} < .001$. 2.2–3.5 ($n = 13$), 3.6–4.4 ($n = 11$), 4.7–6.8 ($n = 17$), 7.2–10.2 ($n = 8$). **B**, Effect of statin use in context of dietary cholesterol ($p < .05$, statin group, covarying diet, serum cholesterol, and gender). No statin: $n = 37$; atorvastin/simvastin (Ator/Sim): $n = 8$; pravastatin/lovastatin (Prav/Lov): $n = 4$. **C** and **D**, Effect of total and low-density lipoprotein (LDL) cholesterol in context of dietary cholesterol ($p < .05$, covarying dietary cholesterol). Total cholesterol (TC) 136–215 ($n = 34$), 216–287 ($n = 15$), LDL 73–120 ($n = 23$), LDL 126–198 ($n = 26$).

$p < .001$) (Figure 1A). Although dietary protein (g/kg lean mass/d) was significantly correlated with dietary cholesterol ($r = 0.387$, $p = .004$), protein was not significantly correlated with change in lean mass ($r = -0.034$, $p = .802$). Other dietary factors, kcal/kg lean mass/d, and mean kilocalories consumed per kilocalories of resting energy expenditure were not significantly correlated with the change in lean mass (18). Only dietary cholesterol entered a stepwise linear regression model ($R^2 = 0.27$, $p < .001$), which evaluated the independent association of major dietary constituents to change in lean mass.

There were also significantly greater lean mass responses in participants using statin medications (Figure 1B) and in participants with higher total (Figure 1C) and LDL (Figure 1D) serum cholesterol. The effect of serum cholesterol and statin use was consistent across levels of dietary cholesterol consumption. The highest mean dietary cholesterol (7.2–10.2 mg/kg lean mass/d) was also associated with greater strength gains (chest press + leg press; 88 ± 14% vs 41 ± 11%, $p = .02$) and appendicular muscle hypertrophy (11.8 ± 2.9% vs 2.6 ± 2.2%, $p = .04$) as compared to the lowest dietary cholesterol (2.2–3.5 mg/kg lean mass/d). Statin use and serum cholesterol were not significantly associated with appendicular muscle or strength gains; however, high-density lipoprotein (HDL) cholesterol was inversely correlated with baseline ($r = -0.36$, $p < .05$) and posttraining ($r = -0.44$, $p < .01$) strength. Dietary cholesterol was not significantly associated with variability in baseline or posttraining serum cholesterol measures ($r < 0.08$). Statin use was not associated with differences in mean dietary cholesterol consumption (statin 4.6 ± 1.4 vs no statin 5.1 ± 2.1 mg/kg lean mass/d).

Dietary cholesterol was not associated with altered markers of cardiovascular risk including serum lipids, plasma hsCRP (Table 2), or blood pressure (Table 3). Trends were observed for higher HDL ($p = .08$) and lower LDL ($p = .07$) in statin users, whereas statin users had a significantly lower ratio of total cholesterol to HDL ($p = .009$). Trends were

Table 2. Serum Markers of Cardiovascular Risk Before and After Resistance Training Stratified by Dietary Cholesterol

	Dietary Cholesterol (mg/kg lean mass/d)			
	2.2–3.5 (N = 7/6)*	3.6–4.4 (N = 6/5)*	4.7–6.9 (N = 5/12)*	7.2–10.3 (N = 5/3)*
	Mean ± *SEM*	Mean ± *SEM*	Mean ± *SEM*	Mean ± *SEM*
Triglycerides, mg/dL				
Pretraining	141.5 ± 17.4	132.5 ± 18.3	128.7 ± 15.4	99.4 ± 21.9
Posttraining	152.3 ± 18.2	136.1 ± 19.1	123.2 ± 16.1	115.5 ± 22.9
Total cholesterol, mg/dL				
Pretraining	193.2 ± 10.0	194.7 ± 10.5	195.1 ± 8.8	208.4 ± 12.5
Posttraining	197.8 ± 12.1	205.5 ± 12.7	197.4 ± 10.7	205.5 ± 15.2
HDL cholesterol, mg/dL†				
Pretraining	43.6 ± 2.8	49.2 ± 3.0	50.8 ± 2.5	52.9 ± 3.5
Posttraining	43.5 ± 2.8	49.0 ± 2.9	50.1 ± 2.4	51.5 ± 3.6
LDL cholesterol, mg/dL‡				
Pretraining	121.4 ± 7.6	119.1 ± 8.0	118.5 ± 6.8	135.6 ± 9.6
Posttraining	124.0 ± 9.5	129.3 ± 9.9	122.7 ± 8.4	130.9 ± 11.9
Total:HDL cholesterol§				
Pretraining	4.34 ± 0.21	3.79 ± 0.22	3.55 ± 0.24	3.63 ± 0.34
Posttraining	4.38 ± 0.25	4.04 ± 0.26	3.77 ± 0.28	3.69 ± 0.41
hsCRP, μg/dL‖				
Pretraining	1.87 ± 1.18	2.51 ± 1.22	4.34 ± 1.15	5.94 ± 1.44
Posttraining	1.89 ± 0.85	2.15 ± 0.88	4.41 ± 0.83	5.11 ± 1.04

Notes: *Ratio of men to women.
†Statins HDL = 54.2 ± 3.4; no statins HDL = 47.8 ± 1.7; $p = .08$.
‡Statins LDL = 109.6 ± 9.7; no statins LDL = 129.9 ± 4.9; $p = .07$.
§Statins total cholesterol:HDL = 3.50 ± 0.24; no statins total cholesterol:HDL = 4.29 ± 0.12; $p = .009$.
‖$p = .08$, dietary cholesterol.
SEM = standard error of the mean; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hsCRP = high sensitivity C-reactive protein.

also observed for increased hsCRP with increasing dietary cholesterol ($p = .08$). Resting supine systolic and diastolic blood pressure were significantly reduced at the end of training (Table 3) and were not affected by medications (data not shown). These reductions were not significantly associated with statin use or dietary cholesterol ($p > .05$).

The independent association of dietary cholesterol, serum cholesterol, and statins with change in lean mass was evaluated by linear regression using the SIMEX package in R (Table 4). Relative dietary cholesterol consumption, total serum cholesterol, and statin use (pravastatin and lovastatin only) were all independently associated with the change in lean mass. Additionally, gender was significantly associated with change in lean mass, as was the interaction between gender and blood cholesterol. This interaction effect suggests that the effect of blood cholesterol is greater in men than in women. Baseline body fat percent, atorvastatin and simvastatin, the interaction of gender and dietary

Table 3. Supine Blood Pressure Before and After Resistance Training Stratified by Dietary Cholesterol

	Dietary Cholesterol (mg/kg lean mass/d)			
	2.2–3.5 (N = 13)	3.6–4.4 (N = 11)	4.7–6.9 (N = 17)	7.2–10.3 (N = 8)
	Mean ± *SEM*	Mean ± *SEM*	Mean ± *SEM*	Mean ± *SEM*
Systolic blood pressure (mmHg, supine)*				
Pretraining	130.6 ± 4.3	125.0 ± 4.0	131.4 ± 3.4	127.4 ± 3.1
Posttraining	126.0 ± 3.7	119.3 ± 3.4	121.0 ± 2.9	119.5 ± 2.9
Diastolic blood pressure (mmHg, supine)†				
Pretraining	76.5 ± 2.3	73.4 ± 2.1	80.2 ± 1.8	79.4 ± 2.5
Posttraining	72.6 ± 2.2	69.8 ± 2.0	73.5 ± 1.7	73.1 ± 1.7
Heart rate (bpm, supine)‡				
Pretraining	67.6 ± 3.1	67.9 ± 2.8	65.4 ± 2.4	69.1 ± 3.6
Posttraining	63.6 ± 3.0	64.1 ± 2.8	66.5 ± 2.4	76.1 ± 2.8

Notes: *Effect of resistance training: $p = .002$. Statins and dietary cholesterol: $p > .05$.
†Effect of resistance training: $p < .001$. Statins and dietary cholesterol: $p > .05$.
‡Effect of resistance training, statins and dietary cholesterol: $p > .05$.
SEM = standard error of the mean.

cholesterol, and the interaction of gender and body fat were not significant. For the model, adjusted $R^2 = 0.448$. The conclusions in terms of which regression coefficients were statistically significant were the same for the regressions with (data not shown) and without (Table 4) measurement errors. When individuals taking statins were excluded from analyses, the model including dietary and serum cholesterol remained significant. Separate analysis by gender confirmed similar trends, although this analysis was not significant.

Table 4. Regression Analysis of the Independent Effect of Dietary Cholesterol, Serum Cholesterol and Statin Use on Change in Lean Mass (kg) With Resistance Training

Variables	Unstandardized Coefficients		
	B	*SE*	*p*
(Constant)	−8.18	2.07	< .001
Dietary cholesterol, mg/kg*	0.58	0.12	< .001
Serum cholesterol, mg/dL	0.03	0.01	.002
Statins, Ator/Sim	−0.05	0.46	.914
Statins, Prav/Lov	2.13	0.64	.002
Obesity, fat mass %	0.03	0.04	.416
Female sex	6.11	2.86	.038
Female sex × Dietary cholesterol	−0.27	0.17	.105
Female sex × Blood cholesterol	−0.02	0.01	.036
Female sex × Obesity	−0.04	0.06	.508

Notes: *mg cholesterol/kg lean mass/d.

SE = standard error; Ator/Sim = atorvastatin, simvastatin; Prav/Lov = pravastatin, lovastatin.

Discussion

It is well accepted that proper nutrition, especially adequate protein, is important to maximize lean mass gains with RET (5,6,13,15,16). When protein consumption was standardized, we observed a strong direct association of dietary cholesterol to the magnitude of lean mass gains that was consistent with the association of serum cholesterol to lean mass gains. This finding was supported by a significant association of dietary cholesterol and change in strength. Moreover, statin users also had greater lean mass gains, independent of dietary and serum cholesterol. This intervention was also associated with significant reductions in systolic and diastolic blood pressure that were not influenced by dietary cholesterol levels.

The results of this study were unexpected given the well-established effects of cholesterol on health and effects of statins on skeletal muscle. It is important to note that a vast majority of these studies do not account for the interaction of these factors with exercise. Nonetheless, we sought alternate explanations for these associations. For example, a sedentary population may have the greatest potential for muscle mass gains, may be more obese, and may consume more cholesterol. However, this is not likely to have affected our results because we selected a population with low physical activity, and obesity was not associated with either dietary cholesterol consumption or muscle gain. The association of cholesterol with other foods, particularly protein, may have also confounded our results. However, we extensively examined protein and found no association with muscle responses. We speculated that this result was due to postexercise protein supplementation (18). It is still possible that a micronutrient such as creatine (not analyzed by our software and known to enhance muscle responses) caused greater muscle mass gains and is also associated to dietary cholesterol (e.g., meat sources). This would not explain the association of blood cholesterol to muscle gain. The well-known limitations of dietary records and their tendency to underestimate intake may be attenuated by the collection of 36 records in 12 weeks. Similar studies typically collect three records at the beginning and at the end of training. This tendency to underestimate dietary intake may be more common in obese individuals; therefore, our failure to identify an association of obesity with muscle gain may have been affected by reporting differences. Even though these results were unexpected, there exists supporting evidence in the literature that cholesterol and statins affect muscle response to RET.

Cholesterol is an essential component of biological membranes. It increases membrane viscosity, which increases the exposure of membrane proteins to extracellular fluids (19). Cholesterol is also essential to the formation of lipid rafts, which function as platforms for the assembly of components of signaling pathways through protein sorting and construction of signaling complexes (20). Cholesterol depletion can induce protein missorting and reduced signal transduction (21,22). Lipid rafts have been implicated as essential for signaling through nitric oxide synthase, protein kinase C-alpha (PKC-α), G-protein α subunits, insulin receptor, insulin-like growth factor-1 (IGF-1) receptor, tumor necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NF-κB), phosphoinositide kinase-3 (PI3K), protein kinase C (PKC), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), interleukin-6 (IL-6), extracellular signal-regulated kinase 2 (ERK2), AKT1, and steroid hormone receptor (21–24). These signaling pathways have been identified as contributors to skeletal muscle adaptation to exercise training (23,24). Thus, one possible explanation for greater skeletal muscle hypertrophy in persons with higher dietary and serum cholesterol is improved cellular signaling as a result of greater membrane cholesterol and signaling assembly through lipid rafts.

Cholesterol may also play a role as an essential building block to repair microtears that occur in the skeletal muscle membrane with RET. However, a readily available supply of circulating cholesterol suggests that this may not be the major mechanism of cholesterol-induced muscle hypertrophy. Immediate reductions in serum cholesterol (within 2 hours, lasting up to 72 hours) following exercise causing muscle injury have been suggested to be part of the process to repair the membrane damage (25,26). These microtears are also associated with an acute immune/inflammatory response that is widely believed to play an important role in skeletal muscle hypertrophy through local production of cytokines and anabolic factors to repair damaged tissue (27).

We observed greater hypertrophy in participants using certain statins. This result was unexpected considering that several studies have reported adverse effects of statins on skeletal muscle (9,27). However, statins increase the

susceptibility of skeletal muscle to membrane injury in response to an acute exercise challenge (28), which may potentiate hypertrophy if the magnitude of this injury and inflammatory response is directly related to the magnitude of hypertrophy through inflammation-related growth factors. Conversely, a decrease in the synthesis of cholesterol intermediates by statins results in a suppression of isoprenoid derivatives essential for prenylation of Ras and Rho GTPases (29). Reduced function of these GTPases has been shown to decrease myocyte proliferation in cell culture, as they are essential for skeletal muscle differentiation and regulate MyoD and myogenin expression (29). The conflicting observations may be explained by differences in in vivo and in vitro experimental protocols and unique complexity of an exercise intervention.

Recently, it has been proposed that statin-induced reduction in the cholesterol synthesis metabolite isopentenyl-pyrophosphate may explain statin myopathy (30). Isopentenylation of selenocysteine-transfer RNA (sec-tRNA) is required for its role in the expression of selenoproteins (31). Selenoprotein N has been linked to myogenesis and myoregeneration, and a genetic mutation in the Selenoprotein N1 (SEPN1) gene results in several forms of congenital juvenile myopathy with similar features to statin-induced myopathy (32). It is interesting that transgenic mice have been developed that reduces selenoproteins through the expression of a dominant mutant form of sec-tRNA. In response to synergistic ablation, a model of exercise overload, these transgenic mice increased muscle mass ~50% more than their wild-type controls (33). Prior to the synergistic ablation, the AKT and $p70^{s6k}$ phosphorylation states were altered and the increased hypertrophy was blocked by the AKT/mammalian target of rapamycin (mTOR) inhibitor rapamycin. Thus statin inhibition of isopentenyl-pyrophosphate and selenoproteins may explain our observed promotion of hypertrophy with statin use.

The direct association between dietary cholesterol and changes in strength further supports the potential anabolic role of cholesterol. Moreover, the significant indirect association of HDL cholesterol with absolute strength both before and after training highlights the potential role of subfractions in the physiology of this response. Whereas the LDL subfraction delivers cholesterol to tissues and is strongly associated with muscle gain, the HDL subfraction delivers cholesterol away from tissues to be metabolized. Previous studies on cholesterol and muscle characteristics are quite limited; however, Kohl and colleagues (34) reported a strong inverse association, consistent with our findings, between HDL and 1 RM strength for chest and leg press (same as in the present report) in 5460 men.

The results of this study suggest that dietary and serum cholesterol contribute to the skeletal muscle response to resistance exercise, conflicting with recommendations to prevent CVD. The evidence that higher serum cholesterol is associated with greater risk for CVD is clear. However, when confounders of dietary assessment were considered, Kritchevsky and Kritchevsky (35) reported that 1 egg per day (210 mg of cholesterol) was not associated with an elevated risk of coronary events whereas only a small 6% increase in risk was associated with a 200 mg/1000 kcal/d difference. The present study demonstrated a significant reduction in systolic and diastolic blood pressure, and there was not a worsening of serum lipid profile with higher dietary cholesterol. However, the trend toward higher hsCRP suggests at least one cardiovascular risk may be elevated.

Sarcopenia is a prevalent and growing economic burden due to its association with chronic disability and mortality. Exercise interventions are efficacious for prevention and treatment of sarcopenia, although recommendations need to be consistent with other diseases associated with age. The current results clearly suggest and are the first to our knowledge to show that higher dietary and serum cholesterol and statin use are independently associated with greater lean mass responses to RET in this group of generally healthy 60- to 69-year-old men and women. Because cholesterol is negatively associated with cardiovascular health, rigorous efforts to confirm these findings are necessary. Even if results are confirmed, it is necessary to examine changes in cardiovascular risk due to dietary cholesterol consumption (within the context of exercise training) so that reduction in sarcopenia and disability is not at the price of elevated CVD.

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Steven E. Riechman is now with Texas A&M University and the University of Pittsburgh.

Ryan D. Andrews is now with The Johns Hopkins Weight Management Center.

David A. MacLean is now with the Northern Ontario School of Medicine.

CORRESPONDENCE

Address correspondence to Steven E. Riechman, PhD, MPH, 149 Read Building, Department of Health and Kinesiology, Texas A&M University, College Station TX, 77843. E-mail: sriechman@hlkn.tamu.edu

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