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Effect of weight loss resulting from a combined low-fat diet/exercise regimen on low-density lipoprotein particle size and distribution in obese women

Krista A. Varady[a], Benoît Lamarche[a], Sylvia Santosa[a], Isabelle Demonty[a], Amélie Charest[b], Peter J.H. Jones[c,*]

[a]School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada, H9X 3V9
[b]Nutraceuticals and Functional Foods Institute, University of Laval, Ste-Foy, Quebec, Canada, G1K 7P4
[c]Richardson Centre for Functional Foods and Nutraceuticals, University of Manitoba, 196 Innovation Drive, Winnipeg, Manitoba, Canada, R3T 6C5

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Abstract

Weight loss resulting from diet interventions has been shown to favorably affect low-density lipoprotein (LDL) particle size and distribution, and, hence, decrease cardiovascular disease risk. However, the effect of a dietary weight loss strategy when combined with exercise, on LDL electrophoretic characteristics, has yet to be tested. This study examined the effect of a weight loss intervention that combined a low-fat diet with moderate endurance training, on LDL particle size and distribution in obese women. Thirty obese, hypercholesterolemic women participated in a controlled longitudinal weight loss trial, which consisted of (1) a 2-week pre-stabilization phase, (2) a 20-week weight loss phase, and (3) a 2-week post-stabilization phase. Weight reduction resulted from a low-fat diet (<30% fat, 50%-60% carbohydrate, 20% protein) combined with an endurance training program (>40 minutes moderate training, 3 times per week). Mean weight loss was 14.8% ($P < .01$) of initial body weight. Total, LDL cholesterol, and triacylglycerol concentrations decreased ($P < .01$) by 8.9%, 7.5%, and 27.1%, respectively, whereas high-density lipoprotein cholesterol concentrations increased ($P < .01$) by 9.9%. No significant differences were noted for LDL peak or integrated particle size. The relative proportion of small, medium, and large particles was not significantly different posttreatment. Estimated cholesterol concentrations in large- and medium-sized LDL particles decreased ($P < .05$) by 15.3% and 5.9%, respectively, as a result of weight loss. No effect was noted for estimated cholesterol concentrations in small size LDL particles. In conclusion, these findings suggest that weight loss, resulting from a low-fat diet/exercise program, has only a minimal effect on LDL particle size and distribution.

1. Introduction

Results from several recent epidemiologic and clinical intervention trials indicate that obesity is a major independent risk factor for cardiovascular disease [1]. Accordingly, weight loss has been shown to favorably affect several indicators of cardiovascular risk, such as plasma lipid [2,3], homocysteine [4], and C-reactive protein [5] concentrations. In addition to these commonly investigated parameters, weight loss has also been shown to beneficially modulate low-density lipoprotein (LDL) size and distribution [6-10]. More specifically, Archer et al [6] demonstrated that a low-fat/high-carbohydrate diet reduced the average body weight of overweight men by 2%, while causing reductions in the cholesterol content of small- and medium-sized LDL particles. Similarly, Markovic et al [7] found that after consuming a low-fat diet for 28 days, mildly obese patients lost an average of 6.2 kg and increased the proportion of large LDL particles in plasma. Furthermore, in a study by Katzel et al [8], it was shown that an average loss of 10 kg of body weight, induced by a low-fat diet, resulted in a significant increase in LDL peak particle diameter. Although these data indicate that diet-induced weight loss positively alters LDL electrophoretic characteristics, the effect of a low-fat diet when placed in combination with exercise, another commonly implemented weight loss strategy, on LDL particle diameter, has yet to be tested. In addition, the

* Corresponding author. Tel.: +1 204 474 8883; fax: +1 204 474 7552.
E-mail address: peter_jones@umanitoba.ca (P.J.H. Jones).

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effect of substantial weight loss, that is, loss of more than 10% of initial body weight, on LDL size and distribution still needs further clarification.

Thus, the objective of the present study was to examine the effect of a 24-week weight loss intervention that combined a low-fat diet with moderate endurance training, on LDL particle size and distribution in obese, hypercholesterolemic women. In addition, the extent to which substantial changes in body weight modulated LDL electrophoretic was also examined.

2. Subjects and methods

2.1. Subjects

Subjects were recruited from the greater Montreal area by means of newspaper advertisements. After a preliminary questionnaire, blood screening, and physical examination, 42 subjects were deemed eligible to partake in the trial. Key inclusion criteria were as follows: nonpregnant women; age of 35 to 60 years; body mass index (BMI) between 28 and 37 kg/m^2; LDL cholesterol (LDL-C) concentrations of greater than 4.5 mmol/L; triacylglycerol concentrations of greater than 1.5 mmol/L; free of cardiovascular disease; free of gastrointestinal, renal, pulmonary, hepatic, or biliary disease; free of cancer; no history of disordered eating; alcohol intake of less than 2 drinks per day; use of fiber or stimulant laxatives of less than 2 doses per week; not taking lipid-lowering medications for the past 6 months; and less than 16 736 kJ/wk (4000 kcal/wk) expended by endurance training. The protocol was approved by the human ethical review committee of the Faculty of Medicine at McGill University (Montreal, Quebec, Canada). Before the commencement of the study, all volunteers gave their written informed consent to participate in the trial.

2.2. Experimental design

A 24-week longitudinal design was implemented as a means of testing the study objectives. Each subject acted as her own control, and therefore, no control group was required [11]. The trial consisted of 3 consecutive dietary periods: (1) a 2-week pre-loss stabilization phase, (2) a 20-week weight loss phase, and (3) a 2-week post-loss stabilization phase. During the first and third phases, subjects were required to maintain a stable weight and were instructed to continue with their usual food habits. In contrast, during the second phase, subjects were required to reduce their energy intake by 20% and increase their energy expenditure by 10%. As a result, target weight loss was approximately 0.75 kg/wk. Premenopausal women started each of the 3 phases at identical points during their menstrual cycles.

2.3. Dietary protocol

Each subject attended individual dietary counseling sessions with a registered dietician or nutritionist on a bi-weekly basis to decrease energy intake by 20% throughout the weight loss phase. During these sessions, volunteers were taught how to attain daily energy goals using an exchange system that provided 50% to 60% of energy from carbohydrates, 20% of energy from protein, and less than 30% of energy from fat. Teaching aids, which outlined the energy contents of commonly ingested food items, as well as sample menus and recipes, were distributed to the volunteers.

2.4. Exercise protocol

As a means of increasing energy expenditure by 10% throughout the 20-week weight loss phase, subjects were instructed to perform moderate aerobic training 3 times per week, for a minimum of 40 minutes. During the trial, each subject met with a personal trainer and was taught proper training techniques and routines. The exercise was performed independently at home or at the Mary-Emily Clinical Nutrition Research Unit.

2.5. Weight loss assessment and compliance

Compliance with both the dietary and exercise protocol was determined by way of weigh-ins that took place once per week throughout the trial. Continuous, regular weight loss throughout the second phase of the study was encouraged by means of a point system as well as visual graphs, which plotted weekly weight changes.

2.6. Blood collection protocol

Twelve-hour fasting blood samples were collected on the mornings of days 0, 13, 14, 15 (phase 1), and 167, 168, and 169 (phase 3) of the trial. Blood was centrifuged for 15 minutes at 520g and 4°C to separate plasma from red blood cells, and was stored at −20°C until analyzed.

2.7. Analyses

2.7.1. Plasma lipid profile determination

Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triacylglycerol concentrations were measured in duplicate by automated methods through a Hitachi 911 automated analyzer (Roche Diagnostics, Indianapolis, IN) using enzymatic or immunoturbidometric reagents [12]. Low-density lipoprotein cholesterol was determined directly by the dextran/magnesium sulfate method to separate it from HDL-C (N-geneous LDL-C assay, Equal Diagnostics, Exton, PA) [13,14].

2.8. Low-density lipoprotein particle size determination

Low-density lipoprotein particle diameter analysis was performed on whole plasma using nondenaturing 2% to 16% polyacrylamide gradient gel electrophoresis [15]. Plasma samples (3.5 μL) were mixed with a sampling buffer containing 20% sucrose and 0.25% bromophenol blue in a 1:1 (vol/vol) ratio. The 6 samples, representing days 13, 14, 15, 167, 168, and 169, for each individual subject were placed on one unique gel. After a 15-minute

prerun, electrophoresis was performed at 150 V for 3 hours. Gels were then stained for 1 hour with Sudan black (0.07%) and stored in a 0.81% acetic acid/4% methanol solution until analysis. The Imagemaster 1-D Prime computer software (Amersham Pharmacia Biotech, Piscataway, NJ) was used to analyze the gels. Mean LDL particle size was computed by integrating the relative contribution of each LDL particle subfraction within a sample and corresponding to the weighted mean of all LDL subfractions. Integrated LDL particle size was calculated as the sum of LDL subspecies' diameter multiplied by its relative proportion. The relative proportion of LDL having a diameter of less than 25.5 nm (termed $LDL\%_{<255\ Å}$) was obtained by computing the relative area of the densitometric scan of less than 25.5 nm. The absolute concentration of cholesterol within the LDL subfraction characterized by a diameter of less than 25.5 nm (termed $LDL\text{-}C_{<25.5\ nm}$) was crudely estimated by multiplying total plasma LDL-C concentrations by $LDL\%_{<25.5\ nm}$ as previously described [15]. A similar approach was used to assess the relative and absolute concentrations of cholesterol in the LDL subfractions with a diameter of more than 26 nm ($LDL\%_{>26\ nm}$ and $LDL\text{-}C_{>26\ nm}$, respectively) and in those with a diameter between 255 and 26 nm ($LDL\%_{25.5\text{-}26\ nm}$ and $LDL\text{-}C_{25.5\text{-}26\ nm}$, respectively).

2.9. Statistics

Results are presented as means ± SEM. A paired *t* test was implemented as a means of comparing baseline and posttreatment weight, lipid, LDL particle size, and distribution values. Pearson correlation coefficients were calculated to test for associations between treatment-induced changes in body weight, plasma lipid concentrations, and LDL electrophoretic characteristics. A level of statistical significance at $P < .05$ was used in all analyses. Data were analyzed using SAS software (version 8.0; SAS Institute, Cary, NC).

3. Results

3.1. Subject baseline characteristics and compliance

Forty-two subjects commenced the study, with 35 completing the entire 24-week trial. The 7 subjects who did not complete the trial dropped out because of an inability to comply with the study protocol. In addition, data from 5 subjects were not analyzed because of plasma sample loss. Therefore, after accounting for these loses, a total of 30 complete subject data sets were used for LDL particle size and distribution analysis. On day 0 of the trial, the mean age, body weight, and BMI of the 30 participants was 48.9 ± 1.24 years, 82.1 ± 1.74 kg, and 31.5 ± 0.52 kg/m^2, respectively. During the weekly meetings with the registered dietician/nutritionist, compliance with the energy-reduced, low-fat diet was reported to be adequate, as demonstrated by proper use of the checklist exchange system. Also during these meetings, reported increases in energy expenditure during the weight loss phase of the study were shown to be satisfactory, as the subjects reported increasing their physical activity levels by a minimum of 120 minutes per week.

3.2. Body weight and plasma lipid profiles

Changes in body weight, BMI, and plasma lipid profiles over the course of the 24-week trial are presented in Table 1. The mean rate of weight loss over the 20-week weight loss phase was 0.59 kg/wk (Fig. 1). From the beginning to the end of the trial, the 30 volunteers experienced a significant ($P < .01$) mean reduction in body weight of 12.0 ± 0.41 kg. When expressed as the difference between day 15 and day 169 values, subjects were shown to have decreased their overall body weight by 14.8%. Body mass index decreased significantly ($P < .01$) from 31.5 to 26.9 kg/m^2 from baseline to posttreatment.

As reported previously [16], plasma lipid parameters were significantly altered as a result of weight loss. Total cholesterol and LDL-C concentrations decreased significantly ($P < .01$) by 8.9% and 7.5%, respectively, after the intervention period. In addition, HDL-C concentrations increased ($P < .01$) by 9.9%, whereas triacylglycerol concentrations decreased by 27.1% from baseline to the end of the trial.

3.3. Low-density lipoprotein peak particle size, integrated size, and distribution

Low-density lipoprotein peak particle size, integrated size, and distribution over the course of the trial are presented in Table 2. No differences were noted with respect to LDL peak particle size from the beginning to the end of the trial. Similarly, no significant differences were noted for LDL integrated size when baseline values were compared with posttreatment values. Furthermore, the relative distributions of cholesterol among small (<25.5 nm), medium (25.5-26 nm), and large (>26 nm) LDL particles showed no significant differences from baseline to posttreatment. However, with respect to the absolute distribution of the different LDL particle subfractions, the estimated

Table 1
Body weight, BMI, and plasma lipid concentrations at baseline and posttreatment

n = 30	Baseline	Posttreatment	% Change	P^a
	Mean ± SEM	Mean ± SEM	Mean ± SEM	
Body weight (kg)	82.14 ± 1.74	70.09 ± 1.71	−14.80 ± 0.52	<.01
BMI	31.53 ± 0.52	26.90 ± 0.52	−14.80 ± 0.52	<.01
Total cholesterol (mmol/L)	6.05 ± 0.16	5.46 ± 0.11	−8.94 ± 1.78	<.01
LDL-C (mmol/L)	3.77 ± 0.12	3.44 ± 0.09	−7.54 ± 2.21	<.01
HDL-C (mmol/L)	1.17 ± 0.04	1.27 ± 0.05	9.92 ± 3.01	<.01
Triacylglycerol (mmol/L)	1.80 ± 0.13	1.25 ± 0.08	−27.14 ± 3.59	<.01

[a] *P* value within group: Student paired *t* test comparing day 15 values to day 169 values.

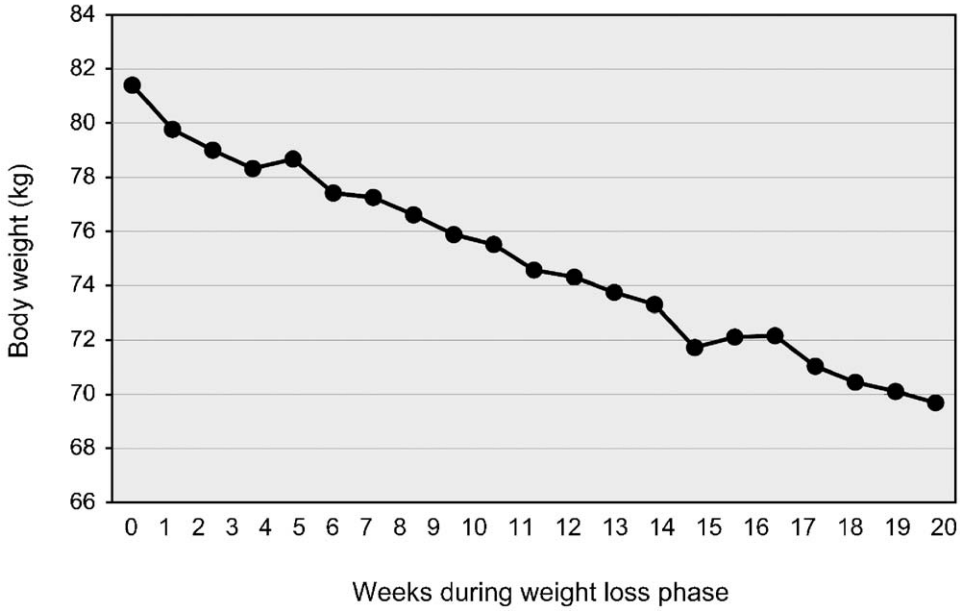

Fig. 1. Body weight reduction during the 20-week weight loss phase. The data presented are the mean body weight values at each week of the trial. The mean rate of weight loss over the 20-week weight loss phase was 0.59 kg/wk. Posttreatment body weight values were shown to be significantly different ($P < .01$) when compared with baseline (Student paired t test).

cholesterol concentration in large-sized LDL particles was shown to decrease significantly ($P < .05$) by 15.3% (0.80-0.68 mmol/L) from the beginning to the end of the trial. In addition, the estimated cholesterol concentration in medium-sized LDL particles was shown to decrease ($P < .05$) by 5.9% (1.39-1.31 mmol/L) posttreatment. No significant changes were noted for the estimated cholesterol concentration in small LDL particles.

3.4. Correlation between body weight and LDL particle size

Body weight has been shown to correlate with variations in LDL particle size and distribution. For this reason, analyses were performed to see if the substantial decrease in body weight resulting from the diet/exercise intervention had an effect on LDL electrophoretic characteristics. Correlational analysis revealed that the greater change in body weight over the course of the trial was associated with increased LDL peak particle size posttreatment ($r = -0.14$, $P = .03$).

3.5. Correlation between triacylglycerol concentrations and LDL particle size

Posttreatment triacylglycerol concentrations were not significantly correlated with any of the posttreatment LDL particle size or distribution parameters measured. In addition, posttreatment triacylglycerol concentrations showed no significant associations with either percent body weight change or posttreatment body weight.

4. Discussion

The results of the present study indicate that a substantial amount of weight loss, that is, loss of approximately 15% of initial body weight, resulting from a low-fat diet combined

Table 2
Low-density lipoprotein peak particle size, integrated size, and distribution at baseline and after a 24-week diet/exercise weight loss intervention

n = 30	Baseline[a]	Posttreatment[b]	% Change[c]	P[d]
	Mean ± SEM	Mean ± SEM	Mean ± SEM	
LDL peak particle size (nm)	25.626 ± .041	25.623 ± .026	−0.01 ± 0.12	.913
LDL integrated size (nm)	25.627 ± .040	25.615 ± .020	−0.05 ± 0.11	.678
LDL%$_{>26\ nm}$ (%)	20.93 ± 2.34	20.07 ± 1.37	−4.12 ± 6.20	.574
LDL%$_{26\text{-}25.5\ nm}$ (%)	36.96 ± 1.47	37.95 ± 1.34	2.68 ± 4.07	.317
LDL%$_{<25.5\ nm}$ (%)	42.26 ± 2.27	42.10 ± 1.81	−0.38 ± 5.36	.909
LDL-C$_{>26\ nm}$ (mmol/L)	0.80 ± 0.10	0.68 ± 0.05	−15.35 ± 7.96	.043
LDL-C$_{25.5\text{-}26\ nm}$ (mmol/L)	1.39 ± 0.07	1.31 ± 0.06	−5.87 ± 3.79	.048
LDL-C$_{<25.5\ nm}$ (mmol/L)	1.58 ± 0.09	1.46 ± .09	−7.82 ± 5.37	.100

[a] Mean of day 13, 14, and 15 values.
[b] Mean of day 167, 168, and 169 values.
[c] Percent change comparing the mean of day 13, 14, and 15 values to the mean of day 167, 168, and 169 values.
[d] P value within group: Student paired t test comparing the mean of day 13, 14, and 15 values to the mean of day 167, 168, and 169 values.

with exercise, decreases the estimated cholesterol concentrations of large and medium LDL particles. The relative proportion of small, medium, and large particles, however, were not significantly altered by this decrease in body weight.

Results of several recent clinical trials show that losing a considerable amount of body weight has favorable effects on certain indicators of cardiovascular disease risk [17-19]. Therefore, it would be expected that in the present intervention trial, which produced a substantial amount of weight loss, certain cardiovascular risk factors such as LDL particle size would be ameliorated. Although such favorable alterations have been previously reported [6-9], the results of the present study demonstrate that this magnitude of weight loss has a minimal effect on LDL particle distribution. More specifically, this study reports a decrease in cholesterol concentrations in both large and medium LDL particles, as a result of a 15% diet/exercise-induced weight reduction. No increase in the cholesterol content of small LDL particles, however, was noted in response to these cholesterol shifts between subfractions. There are several possible explanations that may account for these unexpected findings. First and foremost, these results could partially be explained by the low-fat diet regimen. Recent findings suggest that LDL particles shift from larger, less atherogenic, to smaller, more atherogenic, particles in direct proportion to the degree to which dietary fat is replaced by carbohydrate [20]. Thus, because the subjects were required to lower their fat intake to less than 30% of total energy, and hence, increase their carbohydrate intake to approximately 60% of total energy, it can be assumed that this shift in macronutrient distribution may be responsible for the present findings. Secondly, it is possible that the decrease in cholesterol within large and medium LDL subfractions may be attributed to the physical activity component of the study. More specifically, in a recent study by Varady et al [21], it was demonstrated that participation in a moderate-intensity exercise program decreased the peak particle size of previously sedentary, hypercholesterolemic adults. However, contradictory to these findings [21], other studies that have examined this relationship have reported either an increase in LDL peak particle size as a result of exercise [22-25] or no effect [26]. For instance, in 2 trials [22,23] that examined the effect of endurance training on LDL particle size in obese men, the number of small, dense LDL particles was shown to decrease as a result of training. In line with these findings, Kang et al [24] demonstrated that physical activity had a beneficial effect on LDL particle diameter in obese adolescents. In contrast, Elosua et al [26] demonstrated that after a 16-week training period, no changes were observed with regard to LDL particle diameter in previously sedentary men and women. In view of these findings, because most of the studies in the area suggest a beneficial effect of exercise on LDL electrophoretic characteristics, it is unlikely that the exercise intervention produced these slightly deleterious changes in LDL particle size. Thus, before it can be concluded that exercise is responsible for these unfavorable effects, it is essential that the results of the Varady et al [21] trial be supported by other independent studies testing similar objectives.

Interestingly, correlational analysis revealed a weak but significant association between greater weight loss and an increase peak LDL particle size ($r = -0.14$, $P = .03$).

These associative findings are, evidently, contrary to the causal findings reported in the present article. The reason for these conflicting results is not clear. However, one possible explanation for these contradictory findings may again be the change in diet composition. Because replacing fat with carbohydrate leads to a decrease in particle size, it can be hypothesized that, if this change in diet was not implemented, LDL size may have increased in response to weight loss. Then again, because these findings are merely associative, and also quite weak, these correlational results should not put into question the results of the causative findings. Nevertheless, these contradictory results may suggest that, when attempting to assess the effect of weight loss on vascular disease risk, LDL particle size analysis should be performed in conjunction with other more well-established indicators [27].

In summary, results of the present study demonstrate that a substantial amount of weight loss resulting from a low-fat diet and exercise regimen has no effect on the distribution of small, medium, and large LDL particles. In addition, these data suggest that this weight loss regimen decreases the estimated cholesterol concentrations of large- and medium-sized LDL particles. However, no increase in cholesterol within small LDL particles was observed in response to these cholesterol shifts between subfractions. These findings suggest that low-fat diet/exercise-induced weight loss only minimally affects LDL particle size and distribution. Therefore, when viewed in terms of modulating LDL electrophoretic characteristics, the effect of low-fat diet/exercise-induced weight loss on cardiovascular risk reduction cannot be inferred from the present data.

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