BRIEF OBSERVATION

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Effects of Intense Exercise and Moderate Caloric Restriction on Cardiovascular Risk Factors and Inflammation

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ABSTRACT

BACKGROUND: Obesity is associated with insulin resistance, inflammation, metabolic dysfunction, and atherosclerosis. This study investigates the effects of weight loss, intense exercise, and moderate caloric restriction on insulin resistance, lipids, inflammatory biomarkers, carotid artery distensibility index (CaDI), and carotid intima media thickness (CIMT).

METHODS: Seventeen sedentary morbidly obese contestants in the "Biggest Loser" television program completed the 7-month intense-exercise and moderate-restricting calories program; 3 were excluded due to lack of follow-up CIMT. Serum insulin level, glucose, lipid profile, high-sensitivity C-reactive protein (CRP), hemoglobin A1c (HbA1c), resistin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor receptor-II (TNFRII), lipoprotein a (Lp[a]), sex hormone binding globulin (SHBG), blood pressure, body fat, weight, CaDI, and CIMT were measured at baseline and 7-month follow-up. CIMT was measured 5-10 mm below the common carotid bifurcation during mid-diastolic phase. CaDI was defined as: (End-systole – End-diastole common-carotid cross-sectional area)/(End-diastole common-carotid cross-sectional-area × systemic pulse pressure) × 1000. Insulin resistance was calculated by homeostatic model assessment (HOMA) index.

RESULTS: At 7-month follow-up, major reductions in weight (−39%), body fat (−66%), serum insulin level (−52%), glucose (−21%), high-sensitivity CRP (−81%), HbA1c (−11%), PAI-1 (−49%), TNFRII (−12%), and CIMT (−25%), and increases in CaDI (132%), resistin (344%), adiponectin (94%), Lp(a) (73%), and SHBG (94%) were observed. The improvement in CaDI was positively correlated with increases in adiponectin, Lp(a), SBHG, and resistin ($r^2 = 0.86$, $P = .009$), but inversely with PAI-1, TNFRII, CRP, and IR ($r^2 = -0.64$, $P = .01$). Strong inverse correlation was noted between decreases in CIMT and increases in CaDI ($r^2 = 0.65$, $P = .001$).

CONCLUSION: In morbidly obese individuals, intense exercise with moderate caloric restriction over 7 months is associated with a dramatic improvement in carotid vascular function and atherosclerosis risk factors, as well as a reduction in inflammatory biomarkers, lipids, insulin resistance, and CIMT.

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KEYWORDS: Carotid artery distensibility; Carotid intima media thickness; Inflammation; Intense exercise and moderate caloric restriction; Obesity

Obesity is a chronic condition that is associated with significant morbidity and mortality.[1] Pharmacological and surgical interventions to treat obesity, while useful, are associated with a considerable side-effect profile and financial expense.[2,3]

The beneficial effects of diet-based weight loss on improving the health status of obese patients have been well documented.[4] We investigated the effects of a combined

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intense, long-duration exercise program and moderate caloric restriction on insulin resistance, lipids, inflammatory biomarkers, carotid artery distensibility index (CaDI), and carotid intima media thickness (CIMT) in morbidly obese patients.

MATERIALS AND METHODS

Subject Recruitment

Participants were recruited by television show producers. Applicants who were pregnant, lactating, had prior bariatric surgery, or were receiving anti-obesity drugs were excluded. Seventeen subjects were chosen to be TV contestants, and informed consent was obtained. Three subjects were excluded as they missed their follow-up CIMT. Weight, body fat, blood pressure, glucose, insulin levels, high-sensitivity C reactive protein (CRP), lipid profile, hemoglobin A1c (HbA1c), resistin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor receptor-II (TNFRII), lipoprotein a (Lp[a]), and sex hormone binding globulin (SHBG) were obtained at baseline and 7-month follow-up by standard techniques.

CLINICAL SIGNIFICANCE

- Intense exercise and moderate caloric restriction is the first weight-loss intervention in morbidly obese individuals demonstrating simultaneous improvement in the functional and anatomical burden of atherosclerosis, in addition to favorable effects on body composition, blood pressure, insulin sensitivity, and inflammatory biomarkers.
- Reduction of carotid intima media thickness with this intervention is significantly higher than with statin or niacin therapies.
- Decrease in body fat was greater with this intervention as compared with gastric bypass surgery and 12-month moderate self-monitored physical activity and diet.

Group Exercise and Diet Instructions

"Biggest Loser" contestants were initially housed together; contestants were voted off by their peers every 6-11 days until all were home at 3 months. They received lectures on exercise and general dietary measures including calorie counting. Participants prepared their own food and completed daily food and exercise journals. They exercised 3.3 ± 2.1 hours/day, about half supervised initially. Subjects chose their own calorie intake but were instructed to aim for a protein:carbohydrate:fat ratio of 30:45:25, and to never go below 70% of their resting daily energy expenditure (RDEE) ($21.6 \times$ lean tissue [Kg] + 370).

Carotid Ultrasound Protocol

High-resolution B-mode ultrasound images of the right common-carotid artery were obtained with a 7.5-MHz linear array transducer attached to Philips iE-33 (Philips Medical System, Andover. MA). CIMT was measured 5-10 mm below the common-carotid bifurcation during mid-diastole in the M-mode tracings by automated software and clinically blinded expert readers. The end-systole and end-diastole cross-section area of the common-carotid was calculated with the assumption that the cross-section area is circular (area = $[\text{diameter}/2]^2 \times [\pi]$). CaDI was defined as: CaDI = (End-systole – End-diastole Cross-Sectional-Area of Common-Carotid)/([End-diastole Cross-Sectional Area of Common Carotid] × [systemic-pulse-pressure]) $\times 10^3$.

Statistical Analyses

Target variables had a normal distribution, and Student's t tests were used to assess differences between groups. Generalized linear regression analyses were employed to assess the association of novel markers of atherosclerosis with CaDI and CIMT. The predictive performance, the extent of over-fitting, and generalizability of the model in predicting future outcomes were assessed through internal validation by the bootstrapping method.[5] The power of the study to reject the one-sided null hypothesis was calculated. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board Committee of Cedars-Sinai Medical Center.

RESULTS

The mean age of contestants was 32 ± 11 years, and 50% were female. There was an excellent inter- and intra-observer agreement in measuring CIMT and CaDI (intraclass correlation coefficient = 0.99, $P = .0001$). Compared with baseline values, absolute levels of high-sensitivity CRP, PAI-1, TNFRII, insulin level, glucose, homeostatic model assessment (HOMA), HbA1c, triglyceride, systolic blood pressure, diastolic blood pressure, body weight, body fat, and CIMT decreased significantly at 7 months. In contrast, high-density lipoprotein cholesterol, adiponectin, SHBG, Lp(a), resistin levels, and CaDI increased significantly during the 7-month intervention (Table 1).

Table 2 reveals that after adjustment for risk factors, adiponectin, Lp(a), SHBG, resistin, CRP, HOMA index, TNFRII, mean blood pressure, body fat, and PAI-1 were independent predictors of changes in CaDI ($P < .05$). Table 3 shows that the improvement in CaDI was positively correlated with an increases in adiponectin, Lp(a), SBHG, and resistin ($r^2 = 0.86$, $P = .0001$); but inversely correlated with PAI-1, TNFRII, CRP, mean blood pressure, body fat, and insulin resistance ($r^2 = 0.64$, $P = .0001$). Furthermore, a strong inverse correlation was noted between a decrease in CIMT and an increase in CaDI ($r^2 = 0.65$, $P = .0001$). CIMT decreased proportionally with increasing tertiles of Lp(a) and adiponectin (Figure 1A), as well as decreasing

Table 1 Demographic Characteristics, Conventional and Novel Risk Factors of Subjects with Morbid Obesity at Baseline and 7-Month Follow-up*

Variable	Baseline (n = 14)	Follow-up (n = 14)	Mean Difference	(%) Difference	*P* Value
Common carotid IMT (mm)	0.728 ± 0.194	0.542 ± 0.132	−0.186	−25.5%	.001
ΔCaA*	4.46 ± 2.15	8.28 ± 1.73	3.825	85%	.001
ΔCaA/ED CSA CaA	0.16 ± 0.07	0.34 ± 0.076	0.179	112%	.001
Carotid distensibility index	3.37 ± 1.71	7.83 ± 1.82	4.46	132%	.001
HbA1c	5.77 ± 0.83	5.13 ± 0.48	−0.63	−11%	.008
Insulin level (mIU/mL)	10.23 ± 8.70	4.93 ± 4.61	−5.30	−52%	.08
Glucose (mg/dL)	96.54 ± 16.53	75.92 ± 5.91	−20.61	−21%	.001
HOMA index	2.46 ± 2.24	0.92 ± 0.82	−1.54	−60%	.03
Total cholesterol (mg/dL)	158.46 ± 33.72	182.85 ± 48.42	24.38	15%	.07
Triglyceride (mg/dL)	94.92 ± 54.32	46.23 ± 12.04	−48.69	−52%	.006
LDL-C (mg/dL)	98.85 ± 26.34	119.38 ± 40.66	20.53	21%	.08
HDL-C (mg/dL)	40.38 ± 9.59	53.92 ± 13.84	13.53	33%	.001
High-sensitivity CRP (mg/L)	6.56 ± 2.95	1.28 ± 1.70	−5.28	−81%	.001
PAI-1 (mg/dL)	239.33 ± 51.96	162.80 ± 30.28	−76.53	−49%	.001
TNFRII (mg/dL)	5.17 ± 0.87	4.57 ± 1.21	−0.60	−12%	.001
Adiponectin (mg/L)	2.44 ± 1.16	4.73 ± 1.97	2.29	94%	.0007
SHBG (mg/dL)	31.43 ± 33.70	61.07 ± 30.92	29.6	94%	.05
Resistin (mg/dL)	1.26 ± 0.44	5.55 ± 2.65	4.34	344%	.01
Lipoprotein (a) (mg/dL)	8.93 ± 5.15	15.40 ± 7.21	6.47	73%	.007
Systolic blood pressure	134 ± 9	118 ± 11	−22.8	−17%	.05
Diastolic blood pressure	88 ± 7	73 ± 9	−8.4	−10%	.03
Weight (lbs)	336.5 ± 82.5	203.6 ± 51.9	−132.9	−39.5%	.04
Body fat (%)	48.8 ± 5.4	27.4 ± 9.7	−21.3	−44.1%	.001
Fat (lbs)	164.2 ± 54.1	55.8 ± 29.4	−108.4	−66%	.001

CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; HOMA = homeostatic model assessment; IMT = intima media thickness; LDL-C = low-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor-1; SHBG = sex hormone binding globulin; TNFRII = tumor necrosis factor receptor-II.
ΔCaA: ES CC CSA – ED CC CSA.
ΔCaA/ED CSA CaA: (ES CC CSA – ED CC CSA)/(ED CC CSA).
Carotid Distensibility Index: (ES CC CSA – ED CC CSA)/(ED CC CSA × systemic pulse pressure) × 10^3.
*Accordingly, a 1000× bootstrap resampling procedure yielded very similar results.

insulin resistance and inflammation (Figure 1B). Post hoc power analysis revealed that a sample size of 14 pairs had a power of 0.966 to detect a mean CIMT difference of 0.186 during the 7-month intervention.

DISCUSSION

The current study demonstrates: favorable effects of intense exercise and moderate caloric restriction on body composition, blood pressure control, insulin sensitivity, inflammatory biomarkers, and subclinical carotid atherosclerosis (CIMT); a strong relationship between the decrease in CIMT, vascular function improvement, and changes in insulin resistance and inflammatory biomarkers; a strong inverse association between an increase in CaDI and a decrease in PAI-1, TNFRII, and HOMA independent of conventional risk factors; and a significant direct relationship between an increase in CaDI and an increase in plasma levels of Lp(a),[6] adiponectin,[7] resistin,[8] and SBHG.[9] Similar changes have previously been documented following statin therapy and low-fat diets.[6] These salutary effects have been associated with evidence of concomitant removal of

Table 2 Association of Changes in Inflammatory Biomarkers, Insulin Sensitivity, Blood Pressure and Weight with Improvement in Carotid Artery Distensibility*

Model	Likelihood Ratio	B (95% CI)	*P* Value
Resistin	1.13	1.05-1.34	.02
Lipoprotein (a)	1.31	1.17-1.46	.001
Adiponectin	1.65	1.03-5.84	.04
SHBG	2.88	1.24-6.46	.001
CRP	0.92	0.71-0.99	.04
HOMA	0.83	0.62-0.97	.03
TNFRII	0.52	0.16-0.92	.04
MBP	0.29	0.13-0.64	.001
Body fat (lbs)	0.33	0.10-0.64	.001
PAI-1	0.19	0.09-0.39	.001

CRP = C-reactive protein; HOMA = homeostatic model assessment; MBP = mean blood pressure; PAI-1 = plasminogen activator inhibitor-1; SHBG = sex hormone binding globulin; TNFRII = tumor necrosis factor receptor-II.
Generalized linear regression analysis.
Adjusted for age, sex, conventional risk factors.
*Accordingly, a 1000× bootstrap resampling procedure yielded very similar results.

Table 3 Biochemical and CIMT Changes Associated with CaDI

Model	*r*	r^2	B (95% CI)	*P* Value
Biochemical variables associated with changes in CaDI*				
Model I	0.93	0.86		.009
Adiponectin			0.24 (0.12-0.77)	.02
SHBG			0.19 (0.09-0.98)	.04
Resistin			0.08 (0.03-0.97)	.03
Lipoprotein (a)			0.35 (0.16-0.75)	.003
Model II	−0.81	−0.64		.01
TNFRII			−0.13 (−0.26-−0.05)	.01
PAI-1			−0.26 (−0.48-−0.09)	.01
MBP			−0.06 (−0.19-−0.03)	.01
Body fat (%)			−0.10 (−0.43-−0.04)	.02
HOMA			−0.11 (−0.64-−0.09)	.03
Correlation between changes in common intima media thickness and carotid artery distensibility*				
Model				
CaDI	0.81	0.65	0.81 (0.31-0.89)	.001

CaDI = carotid artery distensibility index; HOMA = homeostatic model assessment; MBP = mean blood pressure; PAI-1 = plasminogen activator inhibitor-1; SHBG = sex hormone binding globulin; TNFRII = tumor necrosis factor receptor-II.
Linear regression analysis; adjusted for age, sex, and cardiovascular risk factors.
*Accordingly, a 1000× bootstrap resampling procedure yielded very similar results.

oxidized phospholipids from the vessel wall and the stabilization of atherosclerosis, as well as positive changes in medium-size low-density lipoprotein particles,[6] and correlate strongly with increases in vascular function and regression in the burden of atherosclerosis.[10]

Changes in CIMT in response to an intense combined exercise and diet program during the 7-month follow-up were significantly higher than statin or niacin therapies (−0.186 vs −0.010, respectively) in the ARBITER 6 trial.[11] Similarly, changes in body weight and fat are substantially greater than individuals who underwent 12-month moderate self-monitored physical activity and diet (weight loss: −39% vs −10%, and fat loss: 66% vs −14%, respectively).[4] Decrease in body fat, but not weight loss, was greater in a combined intense exercise and diet program as compared with gastric bypass surgery (body fat: −47.6% vs −32.7% and weight: −39.5% vs −33.6%, respectively).[12]

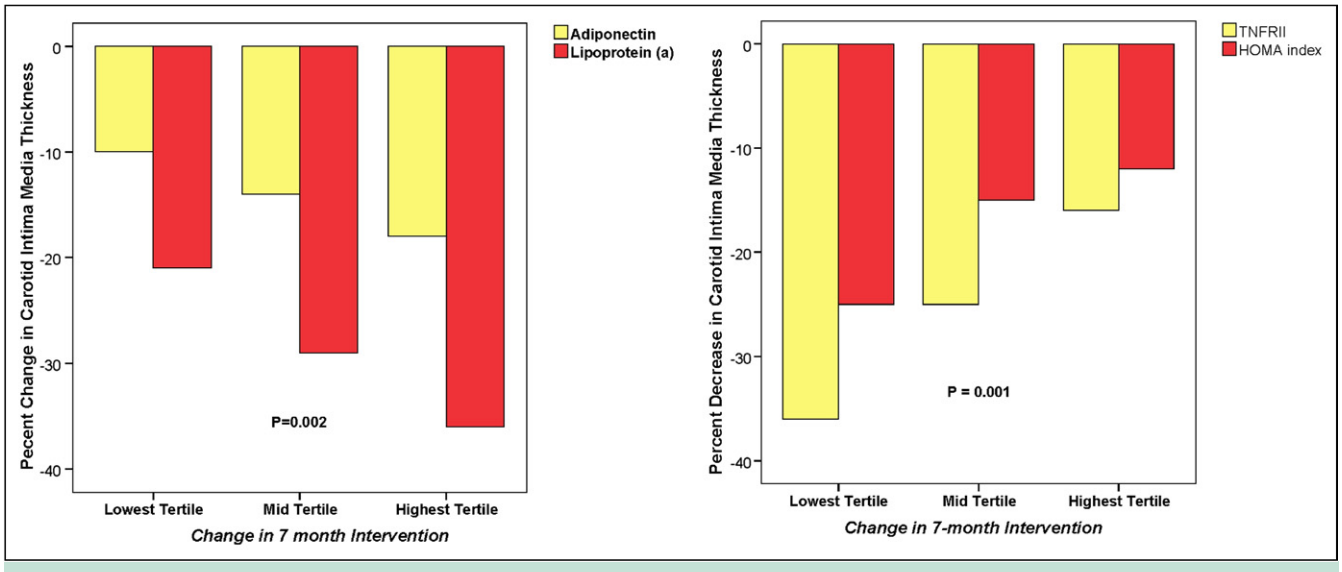

Figure Persistent decrease in carotid intima media thickness with increase in lipoprotein (a) and adiponectin (left), and decreases in insulin resistance and inflammation (right) during the 7-month intense exercise and diet program. HOMA = homeostatic model assessment; TNFRII = tumor necrosis factor receptor-II.

This is the first weight-loss intervention demonstrating simultaneous improvement in the functional and anatomical burden of atherosclerosis. The extent of CIMT improvements—an order of magnitude greater than current statin or niacin therapies—make the atherosclerosis regression potential of intense, high duration exercise and dietary intervention worthy of future clinical trials.

Major limitations of this study include small sample size, sample selection, and lack of control participants.

CONCLUSION

Combined intense exercise and moderate caloric restriction over 7 months in a select group of sedentary morbidly obese individuals result in: regression of CIMT; improvement in vascular function as measured by CaDI; and favorable effects on body composition, blood pressure, insulin sensitivity, lipids, and inflammatory biomarkers.

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