Lifestyle Modification Improves Endothelial Function in Obese Subjects With the Insulin Resistance Syndrome

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OBJECTIVE — Endothelial dysfunction has been reported in type 2 diabetic patients and in obese subjects with insulin resistance syndrome (IRS). This study evaluates the effects of weight reduction and exercise on vascular reactivity of the macro- and the microcirculation in obese subjects with IRS.

RESEARCH DESIGN AND METHODS — We studied 24 obese subjects (9 men and 15 women, age 49.3 ± 1.9 years, BMI 36.7 ± 0.94 kg/m^2, mean ± SEM) with IRS at baseline and after 6 months of weight reduction and exercise. Brachial artery flow-mediated dilation (FMD) and response to sublingual glyceryltrinitrate (GTN) were assessed by high-resolution ultrasound. Microvascular reactivity was evaluated by the laser-Doppler perfusion imaging after iontophoresis of acetylcholine and sodium nitroprusside. We also measured plasma levels of soluble intercellular adhesion molecule (sICAM), vascular adhesion molecule, von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1) antigen, and tissue plasminogen activator antigen.

RESULTS — This intervention resulted in 6.6 ± 1% reduction in body weight ($P < 0.001$) and significant improvement of insulin sensitivity index (2.9 ± 0.36 vs. 1.9 ± 0.33 [$10^{-4} \cdot min^{-1} \cdot (\mu U\ ml^{-1})$], $P < 0.001$). FMD significantly improved (12.9 ± 1.2% vs. 7.9 ± 1.0%, $P < 0.001$), whereas response to GTN and microvascular reactivity did not change. Similar observations were seen when the subjects were subclassified according to their glucose tolerance to normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes. sICAM and PAI-1 significantly decreased (251.3 ± 7.7 vs. 265.6 ± 9.3 ng/ml, $P = 0.018$ and 36.2 ± 3.6 vs. 48.6 ± 3.9 ng/ml, $P = 0.001$, respectively). The relationship between percentage weight reduction and improved FMD was linear ($R^2 = 0.47$, $P = 0.001$).

CONCLUSIONS — We conclude that 6 months of weight reduction and exercise improve macrovascular endothelial function and reduces selective markers of endothelial activation and coagulation in obese subjects with IRS regardless of the degree of glucose tolerance.

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Abbreviations: DBP, diastolic blood pressure; DPP, Diabetes Prevention Program; EF, endothelial function; FMD, flow-mediated dilation; FPG, fasting plasma glucose; GTN, glyceryltrinitrate; IRS, insulin resistance syndrome; sICAM, soluble intercellular adhesion molecule; PAI-1, plasminogen activator inhibitor-1; S_i, sensitivity index; sVCAM, soluble vascular cell adhesion molecule; TC, total cholesterol; VR, vascular reactivity; vWF, von Willebrand factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Obesity and insulin resistance are often associated with hyperinsulinemia, glucose intolerance, hypertension, dyslipidemia, premature atherosclerosis, and increased risk for coronary artery disease (1). This cluster of abnormalities is known as the insulin resistance syndrome (IRS) or the metabolic syndrome (2). According to the recently suggested Adult Treatment Panel-III clinical guidelines of the National Cholesterol Education Program, it is estimated that the age-adjusted prevalence of the metabolic syndrome is ~23.7% of the adult population (3). This population has an overall excess coronary artery disease risk of ~70% (4).

Endothelial dysfunction, an early step in the development of atherosclerosis (5), has been reported in patients with type 2 diabetes (6) and in obese nondiabetic individuals (7). It also exists in subjects at high risk for developing diabetes, including subjects with impaired glucose tolerance and normoglycemic first-degree relatives of patients with type 2 diabetes (8).

Lifestyle modification in the form of caloric restriction and increased physical activity are the most common modalities used for treating obese individuals with IRS. Recently, the Diabetes Prevention Program (DPP) showed that lifestyle modification that achieved 5–7% weight reduction, which was sustained for an average duration of 2.8 years, reduced risk for developing diabetes by 58% among subjects with impaired glucose tolerance compared with the control group (9). Although, both weight reduction and physical exercise training are known to improve insulin sensitivity, few data are available on the effects of these interventions on vascular reactivity (VR) and endothelial function (EF) and on plasma markers of endothelial activation and markers of coagulation in obese individuals with IRS (10,11). This study was conducted to test the hypothesis that a 6-month program of weight reduction achieved by caloric restriction in combi-

nation with moderate intensity physical exercise, similar to that used in the lifestyle intervention arm of the DPP, would improve VR and EF of the macrocirculation (as the primary end point) and improve VR of microcirculation and reduce plasma levels of key markers of endothelial activation and markers of coagulation (as secondary end points) in obese subjects with insulin resistance.

RESEARCH DESIGN AND METHODS

— This 6-month intervention study was designed with a weight reduction goal similar to the intensive lifestyle intervention arm of the DPP (9), which is a weight reduction of 7% of the initial body weight. All the included subjects were obese (BMI between 30 and 40 kg/m^2) with age ranging between 30 and 65 years and with insulin sensitivity index (S_i) <5 [$10^{-4} \cdot min^{-1} \cdot (\mu U\ ml^{-1})$]. We planned to have a total of 24 subjects complete the intervention program, 8 with normal glucose tolerance, 8 with impaired glucose tolerance, and 8 with type 2 diabetes to satisfy the statistical power for subanalysis according to glucose tolerance. To achieve that targeted number, dropouts were replaced, and a total of 35 subjects were recruited. Seven subjects did not continue the protocol for unspecified reasons and could not be reached for follow-up, one was unable to meet the time commitment to exercise at the Joslin gymnasium, one discontinued because of broken ribs, another had knee surgery, and one moved away from the area. Diagnosis of impaired glucose tolerance was made if fasting plasma glucose (FPG) was ≤125 mg/dl and 2-h plasma glucose was between 140 and 199 mg/dl during a 75-g standard oral glucose tolerance test, whereas type 2 diabetes was defined as FPG ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl. Included subjects did not participate in any regular exercise program for at least 6 months before the beginning of this study.

Subjects were excluded if they had a history of smoking during the previous 6 months or if they had a history of cardiovascular disease (angina pectoris, recent myocardial infarction, history of coronary artery bypass surgery or angioplasty, congestive heart failure, or arrhythmia), stroke, or transient ischemic attacks. Other exclusion criteria include total cholesterol (TC) >300 mg/dl, triglycerides >600 mg/dl (untreated or treated), blood pressure >160/100 mmHg (untreated or treated), FPG >300 mg/dl, or HbA_{1c} >11%. Subjects with diabetic proliferative retinopathy, nephropathy (albumin excretion >300 μg/mg creatinine and/or serum creatinine >2.0 mg/dl), signs or symptoms of diabetic autonomic or peripheral neuropathy, and diabetic patients on either insulin or thiazolidendiones were also excluded. Patients on metformin were allowed to participate in the study after a washout period of 1 month, providing that their FPG did not exceed 250 mg/dl at the beginning of the study. Diabetic patients on sulfonylureas were accepted into the study providing that the dose of sulfonylureas remained constant throughout the intervention period. The study did not include any subject on ACE inhibitors, angiotensin receptor blockers, glucocorticoids, antineoplastic agents, or psychoactive medications.

Lifestyle interventions

The study was approved by the Institutional Review Boards of both the Joslin Diabetes Center and the Beth Israel Deaconess Medical Center. Each participant signed the study consent form before enrollment in the program. All eligible participants entered an intensive lifestyle modification program consisting of caloric restriction and a structured exercise program. They followed a balanced low-calorie diet plan (500 calories/day negative energy balance) under supervision of the study nutritionist. They were also asked to keep dietary records and were contacted by phone on a regular basis. Meanwhile, they were also seen once a month for dietary evaluation. At each visit, the study nutritionist assessed their compliance and reinforced their weight reduction goals and recommendations. All participants exercised three times per week (30 min each) at 60–80% of their maximal heart rate at the Joslin Diabetes Center Gymnasium, under close supervision of four exercise physiologists, and at home during the rest of the week for a total of at least 150 min/week. Before beginning the exercise programs, each participant was interviewed for 40–45 min by one of the study exercise physiologists. A complete health and exercise history was taken, and general exercise information was reviewed with each participant. This information was used to individualize the exercise prescription. The exercise program was designed to involve both upper and lower limbs.

Assessments

Assessments of VR and EF in the macrocirculation and the microcirculation were done at baseline and at the end of the 6 months of intervention.

Vascular reactivity tests. To evaluate the endothelium-dependent reactivity in the macrocirculation, the flow-mediated dilation (FMD) of the brachial artery was measured using the high-resolution vascular ultrasound (Advanced Technology Laboratories, Bothell, WA) using a 10-MHz linear array transducer. Reactive hyperemia is produced by inflating a pneumatic tourniquet 2 cm below the antecubital fossa to occlude the artery for 5 min and then deflating it. This procedure is described in detail elsewhere (12). To evaluate the endothelium-independent vasodilation, the brachial artery was scanned before and 5 min after sublingual administration of 400 mg of glyceryltrinitrate (GTN) spray. Fifteen minutes were allowed for the brachial artery to return to baseline between the two tests. This technique has a coefficient of variability of ~15% in our laboratory.

Microvascular reactivity was evaluated by the laser doppler perfusion imaging technique after iontophoresis of acetylcholine and sodium nitroprusside into the forearm skin, as previously described (13). This technique had been validated against direct measurements of the capillary flow velocity (14).

Both the micro- and macrovascular study procedures were conducted at the microvascular research laboratory of the Beth Israel Deaconess Medical Center (west campus), whereas the analysis of brachial artery measurements was done at the Clinical Research Section of the Joslin Diabetes Center using the Scion Image software (based on NIH Image by Wayne Rashband [wayne@helix.nih.gov] of the National Institute of Health). Image enhancer, edge finder, and color conversion capabilities of the software were used to define the intimal lines for accurate measurement of the actual lumen diameter. Of the 24 subjects, we were able to analyze the paired FMD scans in 22 subjects and the post-GTN scans in 20 subjects.

Evaluation of endothelial activation and coagulation markers. Von Willebrand factor (vWF) (Asserachrom; American Bioproducts, Parsippany, NJ),

Table 1—*The baseline characteristics of the entire group and the three subgroups that participated in lifestyle modification program*

	Whole group	NGT	IGT	Type 2 diabetes	*P*
n	24	8	8	8	
Age (years)	49.3 ± 1.9	47.6 ± 3.0	51.4 ± 3.4	48.9 ± 3.7	NS
Weight (kg)	106.1 ± 3.7	103.8 ± 6.3	104.9 ± 9.1	108.2 ± 6.6	NS
BMI (kg/m^2)	36.7 ± 0.9	36.7 ± 0.9	36.4 ± 2.3	36.3 ± 2.2	NS
Waist-to-hip ratio	0.92 ± 0.02	0.87 ± 0.04	0.91 ± 0.03	0.97 ± 0.03	NS
Systolic BP (mmHg)	127.1 ± 2.8	127.3 ± 4.1	127.0 ± 5.4	127.0 ± 5.4	NS
DBP (mmHg)	80.4 ± 2.0	80.8 ± 3.6	78.3 ± 3.5	82.3 ± 3.8	NS
FPG (mg/dl)	129.6 ± 9.7	96.8 ± 2.1	111.6 ± 4.5	152.6 ± 25.9	<0.05
HbA_{1c} (%)	6.1 ± 0.3	5.3 ± 0.1	5.4 ± 0.2	7.6 ± 0.5	<0.05
TC (mg/dl)	194.0 ± 5.8	191.5 ± 8.2	189.8 ± 11.8	200.8 ± 10.7	NS
Serum triglycerides (mg/dl)	155.5 ± 18.7	150.3 ± 33.4	144.5 ± 34.5	171.9 ± 32.7	NS
LDL cholesterol (mg/dl)	117.3 ± 5.4	116.8 ± 6.1	110.5 ± 11.5	124.6 ± 10.3	NS
HDL cholesterol (mg/dl)	48.6 ± 1.8	49.3 ± 3.1	52.0 ± 3.7	44.5 ± 2.5	NS
$S_i\ 10^{-4}\ min^{-1} \cdot (mU/ml)^{-1}$	1.9 ± 0.3	2.1 ± 0.3	2.2 ± 0.8	1.2 ± 0.6	NS

Data are means ± SEM. BP, blood pressure; NGT, normal glucose tolerance; IGT, impaired glucose tolerance. Sign *P* value using three-way ANOVA test. NS, not significant. For conversion to SI units multiply by 0.05551 for glucose, by 0.01129 for triglycerides, and by 0.02586 for cholesterol, LDL, and HDL.

soluble vascular cell adhesion molecule (sVCAM), and soluble intercellular adhesion molecule (sICAM) (R&D Systems, Minneapolis, MN) were measured in plasma in duplicate using the enzyme-linked immunosorbent assay method. Plasminogen activator inhibitor-1 (PAI-1) antigen and tissue plasminogen activator (t-PA) antigen were measured using the immulite method and commercial kits. All assays were done at the core laboratory of the General Clinical Research Center of the Beth Israel Deaconess Medical Center (Boston, MA).

Evaluation of insulin sensitivity. We used the frequently sampled intravenous glucose tolerance test and the minimal model protocol developed by Bergman et al. (15) for evaluation of the insulin S_i.

Statistical analysis

Changes in VR in the brachial artery and in the skin microcirculation were expressed as the mean percentage change over baseline ± SEM. Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. Two-sided paired Student's *t* test (for parametric data) and Kruskal-Wallis test (for nonparametric data) were used to compare baseline versus postintervention values. Pearson correlation, linear regression analysis, and multiple regression analysis were used to demonstrate the relationship between changes in VR and the changes in other continuous measurements (S_i, HbA_{1c}, glucose, and insulin area under the curve during the oral glucose tolerance test, serum lipids, blood pressure, BMI, and waist-to-hip ratio). $P < 0.05$ (by two-tailed testing) was considered an indicator of statistical significance. Analysis of data were done using SPSS statistical package for Windows (SPSS, Chicago, IL).

RESULTS — The mean age of the group studied (9 men and 15 women) was 49.3 ± 1.9 (mean ± SEM), and their mean weight was 106.1 ± 3.7 kg and BMI 36.7 ± 0.9. All included subjects were insulin resistant with an average S_i of $1.9 + 0.3\ 10^{-4}\ min^{-1} \cdot (mU/ml)^{-1}$. Subdividing this entire group at baseline according to glucose tolerance did not show any significant differences among the three subgroups except for FPG and HbA_{1c} (Table 1). At baseline, there were no statistical differences between those who completed the intervention program and those who dropped out.

After 6 months of lifestyle modifications, the mean weight reduction was −7.1 ± 1.2 kg (−6.6 ± 1.0% of the initial body weight, $P < 0.001$). BMI decreased from a mean of 36.7 ± 0.9 to 34 ± 1.1 kg/m^2 ($P < 0.001$). Changes in all other parameters are summarized in Table 2.

Brachial artery FMD improved from 7.9 ± 1 to 12.9 ± 1.2% ($P < 0.001$). Comparable improvements were seen when the included subjects were subclassified according to their glucose tolerance into those with normal glucose tolerance, impaired glucose tolerance, and type 2

Table 2—*Changes in metabolic and anthropometric parameters before versus after lifestyle modification for 6 months*

	Before	After	*P*
Systolic BP (mmHg)	127.1 ± 2.8	124.8 ± 2.7	NS
DBP (mmHg)	80.4 ± 2.0	74.8 ± 2.6	NS
Serum TC (mg/dl)	194.0 ± 5.8	192.0 ± 6	NS
Serum triglycerides (mg/dl)	155.5 ± 18.7	130.6 ± 18.4	NS
LDL cholesterol (mg/dl)	117.3 ± 5.4	116.1 ± 4.7	NS
HDL cholesterol (mg/dl)	48.6 ± 1.8	53.0 ± 2.1	0.008
FPG (mg/dl)	129.6 ± 9.7	117.4 ± 6.3	NS
HbA_{1c} (%)	6.1 ± 0.3	5.8 ± 0.2	0.008
$S_i\ 10^{-4}\ min^{-1} \cdot (mU/ml)^{-1}$	1.9 ± 0.3	2.9 ± 0.4	<0.001
Weight (kg)	106.1 ± 3.7	98.7 ± 3.8	<0.001
BMI (kg/m^2)	36.7 ± 0.9	34.0 ± 1.1	<0.001
Waist-to-hip ratio	0.92 ± 0.02	0.89 ± 0.02	<0.001

Data are means ± SEM. BP, blood pressure; NS, not significant. For conversion to SI units multiply by 0.02586 for cholesterol, LDL, and HDL, by 0.01129 for triglyceride, and by 0.05551 for glucose.

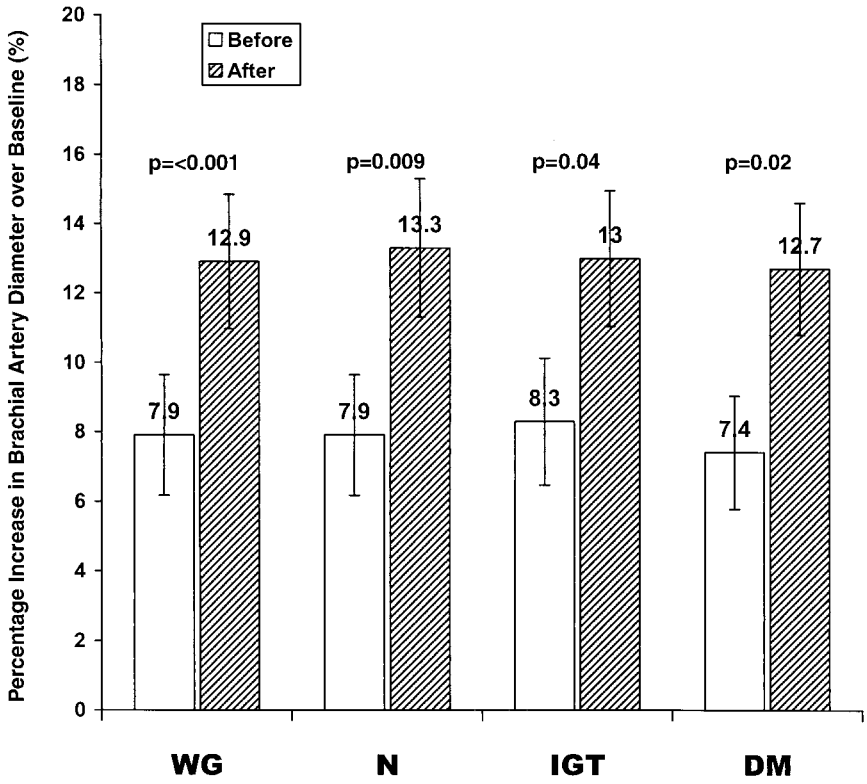

Figure 1—*Percentage increase over baseline in the FMD of the brachial artery after 6 months of lifestyle modification in the whole group studied (WG), in subjects with normal glucose tolerance (N), impaired glucose tolerance (IGT), and type 2 diabetes (DM).*

diabetes (Fig. 1). The GTN-induced dilation of the brachial artery and the endothelium-dependent and endothelium-independent function of the forearm-skin microcirculation did not change significantly (Table 3).

Among the endothelial and coagulation markers that were measured in this study, sICAM showed significant reduction (251.3 ± 7.7 vs. 265.6 ± 9.3 ng/ml, $P = 0.018$), but the plasma concentrations of sVCAM and vWF did not change significantly. PAI-1 antigen significantly decreased (36.2 ± 3.6 vs. 48.6 ± 3.9 ng/ml, $P = 0.001$), whereas the decrease in plasma t-PA antigen was not significant (8.5 ± 1.2 vs. 8.9 ± 1.1, $P > 0.05$) (Table 3).

Multiple regression models were constructed to identify the predictors of the improved brachial FMD. We initially tested the covariates that showed association with the improved FMD or those variables that have clinical relevance to the outcome. In the final backward elimination model, percentage reduction in body weight, reduction in FPG, reduction in serum TC, and reduction in diastolic blood pressure (DBP) were the only significant variables retained. Adding the improvement in insulin sensitivity into the model, for its clinical relevance, improved its predictive value ($R^2 = 0.72$, $P = 0.005$). After adjustment for the FPG, TC, DBP, and S_i in the final regression model, the percentage weight reduction remained a significant predictor of improved brachial FMD ($P = 0.009$). The relationship between the percentage weight reduction and the percentage improvement in the brachial FMD was linear ($R^2 = 0.47$, $P = 0.001$) (Fig. 2). Similar relationship was observed between the change in the BMI and percentage change in brachial FMD ($R^2 = 0.29$, $P = 0.01$).

CONCLUSIONS — The principal finding of this study is that a 6-month program of lifestyle modification in the form of caloric restriction and moderate intensity physical exercise in obese subjects with the IRS significantly improved endothelium-dependent vasodilation of the brachial artery. This improvement was observed across the entire spectrum of glucose tolerance and was strongly associated with the percentage weight reduction. This effect was also associated with significant reduction in the plasma levels of selective markers of endothelial activation and coagulation. Meanwhile, this program did not improve the endothelium-independent vasodilation of the brachial artery and did not change the endothelium-dependent or endothelium-independent vasodilation of the forearm-skin microcirculation. The study also demonstrated that the main predictors of improved brachial FMD are percentage

Table 3—*Changes in vascular reactivity of the macro- and the microcirculation and the key markers of endothelial activation and coagulation before versus after lifestyle modification for 6 months*

	Before	After	*P*
Brachial artery diameter (baseline) (mm)	3.87 ± 0.16	4.07 ± 0.18	NS
Brachial artery diameter (FMD) (mm)	4.17 ± 0.17	4.59 ± 0.2	<0.01
FMD of brachial artery (% increase over baseline)	7.9 ± 1.0	12.9 ± 1.2	<0.001
Brachial artery diameter (baseline) (mm)	4.02 ± 0.21	4.13 ± 0.18	NS
Brachial artery diameter (GTN) (mm)	4.55 ± 0.20	4.70 ± 0.18	NS
GTN-induced VD of brachial artery (% increase over baseline)	14.1 ± 1.9	14.4 ± 1.6	NS
ACH (% increase over baseline)	62.9 ± 7.6	60.9 ± 8.0	NS
SNP (% increase over baseline)	42.4 ± 5.6	37.4 ± 3.6	NS
vWF (ng/ml)	114.6 ± 6.6	113.8 ± 8.0	NS
sICAM (ng/ml)	265.6 ± 9.3	251.3 ± 7.7	0.018
sVCAM (ng/ml)	444.3 ± 20.56	443.7 ± 22.9	NS
PAI-1 (ng/ml)	48.6 ± 3.9	36.2 ± 3.6	0.001
t-PA (ng/ml)	8.9 ± 1.1	8.5 ± 1.2	NS

Data are means ± SEM. ACH, acetylcholine-induced increase in skin blood flow; SNP, sodium nitroprusside-induced increase in skin blood flow; VD, vasodilation.

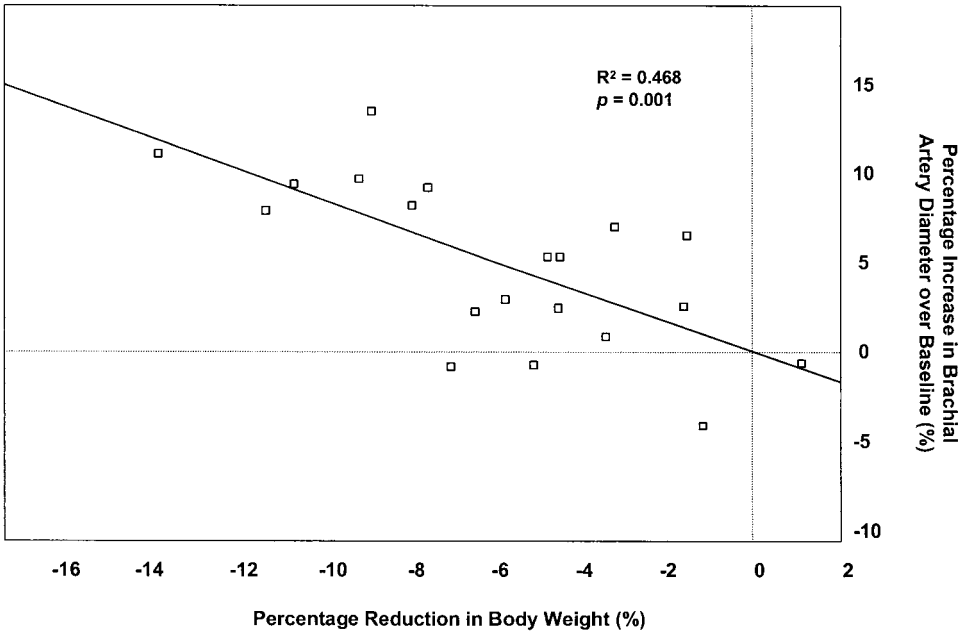

Figure 2—*Relationship between the percentage increase over baseline in the FMD of the brachial artery and the percentage reduction in body weight in obese subjects with IRS after 6 months of lifestyle modification.*

reduction in body weight, reduction in FPG, serum TC, and DBP, and improvement of insulin sensitivity.

To our knowledge, only one prior study has evaluated the effect of weight reduction with and without exercise on vessel wall properties of the brachial and common carotid arteries in obese, but otherwise healthy, men (10). Using a vessel wall movement detector, this 3-month study showed that weight loss increased carotid artery distensibility but found no additional benefit from adding an exercise component to the weight loss program. In contrast, improvement in macrovascular endothelium-dependent vasodilation was reported after acute (16) and chronic exercise programs (11,17) that did not include a weight reduction component. One study (11) found that 3 months of physical training enhanced brachial artery FMD in patients with the polymetabolic syndrome, and a second study (17) observed that 12 weeks of aerobic and resistance training improved brachial artery FMD in subjects with type 2 diabetes. Similar favorable effects of exercise training on FMD were also seen more recently in a group of long-standing type 1 diabetic patients (18). On the other hand, weight loss alone through weight-reducing gastroplasty was associated with reduced progression rate of carotid intima-media thickness over 4 years (19). Another recent study showed that caloric restriction enhanced the response of forearm blood flow to acetylcholine in obese hypertensive Japanese subjects but did not alter the response to isosorbide dinitrate. The intra-arterial infusion of NG-monomethyl-L-arginine, a nitric oxide synthase inhibitor, decreased the enhanced acetylcholine-induced blood flow response induced by caloric restriction (20).

In the current study, we used a different design of combined diet restriction and moderate intensity exercise similar to the lifestyle intervention arm of the DPP and with similar weight reduction target (9). As expected, this 6-month program resulted in a reduction in body weight and BMI that was comparable with that achieved in the DPP study (9) and was associated with significant improvement in S_i, HDL, and HbA_{1c} (Table 2). In addition, we have studied obese subjects (BMI $>$ 30 kg/m^2) with insulin resistance across a range of glucose tolerance. We found that the improvement in the brachial FMD was similar in the three subgroups. Although the study did not include a healthy lean group, the reported FMD at the end of this program is similar to changes seen in other lean populations using the same technique (8). This may indicate a restoration of EF to normal after lifestyle modification, but it is not clear if this effect would be maintained after cessation of the intervention program. One study showed that the vascular effects from exercise training were abrogated 8 months after cessation of exercise (18).

The current study did not differentiate between the effects of weight reduction versus the effects of exercise. One study in type 2 diabetic rats found that exercise training, but not food restriction, prevents endothelial dysfunction, although both interventions significantly suppressed plasma levels of glucose, insulin, cholesterol, and reduced the accumulation of abdominal fat and improved insulin sensitivity to a comparable extent (21). Similar studies in humans are still lacking.

One potential weakness of the present study is the lack of a control group, and it is possible that studied subjects may have been acclimatized to the experimental conditions, resulting in some improvement in FMD independent of the intervention per se. However, in other studies we have observed only minimal increases in FMD response over time in control subjects (unpublished data). It is also noticeable that the average baseline artery diameter was slightly increased. Such change was minimal and statistically nonsignificant and should not affect the percentage response with intervention.

In agreement with previous studies (22,23), this intervention did not have any significant effect on the endothelium-independent vasodilation of the brachial artery, a mechanism confined solely to vascular smooth muscle cell function.

Our results also demonstrate that lifestyle modification has no significant effect on the endothelium-dependent or endothelium-independent vasodilation of the forearm skin microcirculation. The observation that macrovascular improvement was not associated with microvascular improvement is quite important and was an unanticipated finding. Currently, we do not have a good explanation for this variability in response. One possibility is that conduit vessels have different characteristics in sensitivity to insulin compared with microcirculation (24). Additional studies are clearly needed to evaluate this observation.

Along with the improved brachial FMD, we observed a significant reduction in plasma concentration of sICAM. This finding is consistent with a similar recent observation by Ziccardi et al. (25) in obese premenopausal women after weight reduction for 1 year. Circulating soluble adhesion molecules are valuable markers of atherosclerosis, and particularly the elevated sICAM levels were found to be associated with increased risk of future myocardial infarction in healthy men (26). The reduction in sICAM in our study population was not associated with significant changes in sVCAM and vWF. One possible explanation is that plasma sICAM levels were reported to be particularly higher in hyperglycemic subjects (27), whereas sVCAM concentrations had been found to be particularly elevated in hypertriglyceridemic subjects, including children (28). Our study population, by the inclusion criteria, was not hypertriglyceridemic at baseline with mean serum triglycerides of 155.5 ± 18.7 mg/dl. This may explain the relatively low baseline levels of sVCAM in this study. Meanwhile, a recent study showed that elevated levels of sICAM and not sVCAM are independently associated with the development of accelerated atherosclerosis among otherwise healthy men (29). Although vWF concentrations are elevated in type 2 diabetic patients, they were reported to be weakly related to features of the IRS and unrelated to BMI (30); consequently the improvement of insulin resistance and the reduction of BMI in this study may not be necessarily associated with reduction in vWF plasma levels.

We also observed a significant reduction in the plasma PAI-1 antigen, indicating an improvement in fibrinolytic system with weight reduction. This cytokine was shown to be elevated in insulin-resistant state and correlates with the degree of visceral adiposity (31). Likewise, Rissanen et al. (32) observed significant reduction in PAI-1 after 6 months of weight reduction in obese healthy women. They also found that this reduction correlated with the magnitude of weight loss and tended to rise with weight rebound but remained below the 6-month values if the weight loss was sustained or continued (32). Considering that PAI-1 is a cytokine that is expressed in adipose tissue and vascular endothelium, this observation could be of particular importance as it supports the postulated relationship of inflammation and endothelial activation with insulin resistance and adiposity (33).

We conclude that a program of caloric restriction and moderate intensity physical exercise for as short as 6 months improves EF of the brachial artery, decreases endothelial activation, and has positive impact on the fibrinolytic system in obese subjects with IRS regardless of the degree of glucose tolerance. The improvement in brachial FMD is strongly associated with the percentage weight reduction and could be predicted by the magnitude of the reduction in body weight, FPG, TC, DBP, and the improvement in insulin sensitivity. These findings provide additional evidence that similar programs not only decrease the risk of developing type 2 diabetes, as demonstrated earlier in the DPP (9) and other lifestyle intervention studies, but also improve EF and may ultimately decrease the risk of atherosclerosis and cardiovascular disease in obese subjects with IRS.

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