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CME

Insulin Status and Vascular Responses to Weight Loss in Obesity

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Insulin Status and Vascular Responses to Weight Loss in Obesity

Objectives The aim of this study was to determine whether the effects of weight loss on arterial function are differentially modified by insulin status.

Background Clinical studies suggest that plasma insulin levels may predict the extent of cardiovascular benefit achieved with weight loss in obese individuals, but mechanisms are currently unknown.

Methods We prospectively followed 208 overweight or obese patients (body mass index [BMI] $\geq$25 kg/m^2) receiving medical/dietary (48%) or bariatric surgical (52%) weight-loss treatment during a median period of 11.7 months (interquartile range: 4.6 to 13 months). We measured plasma metabolic parameters and vascular endothelial function using ultrasound at baseline and following weight-loss intervention and stratified analyses by median plasma insulin levels.

Results Patients age 45 $\pm$ 1 years, with BMI 45 $\pm$ 9 kg/m^2, experienced 14 $\pm$ 14% weight loss during the study period. In individuals with higher baseline plasma insulin levels (above median >12 μIU/ml; n = 99), $\geq$10% weight loss (compared with <10%) significantly improved brachial artery macrovascular flow-mediated vasodilation and microvascular reactive hyperemia ($p < 0.05$ for all). By contrast, vascular function did not change significantly in the lower insulin group ($\leq$12 μIU/ml; n = 109) despite a similar degree of weight loss. In analyses using a 5% weight loss cut point, only microvascular responses improved in the higher insulin group ($p = 0.02$).

Conclusions Insulin status is an important determinant of the positive effect of weight reduction on vascular function with hyperinsulinemic patients deriving the greatest benefit. Integrated improvement in both microvascular and macrovascular function was associated with $\geq$10% weight loss. Reversal of insulin resistance and endothelial dysfunction may represent key therapeutic targets for cardiovascular risk reduction in obesity. (J Am Coll Cardiol 2013;62:2297–305) © 2013 by the American College of Cardiology Foundation

Obesity has emerged as one of the most critical healthcare problems in the United States and worldwide, with nearly 70% of the U.S. population currently overweight or obese (1). Of major concern are data showing disproportionate surges in categories of severe obesity (body mass index [BMI] $\geq$40 kg/m^2), which tripled its prevalence during the 1990s (2). Nearly one-third of adults (1) and 17% of children (3) in the United States are now obese, with 65 million additional cases estimated by 2030 (4). Although obesity confers serious health concerns and increased all-cause mortality, the vast majority of deaths are due to cardiovascular causes such as ischemic heart disease and stroke (5,6).

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Thus, there is a pressing need to elucidate potential mechanisms that link excess adiposity to cardiovascular risk and identify groups most likely to benefit from targeted treatment.

Although obesity prevention is likely to provide the optimal public health solution, there is obvious interest in promoting weight loss as a therapeutic strategy to reverse obesity-related cardiometabolic risk (5). However, few clinical studies have explicitly examined the relationship between intentional weight loss and cardiovascular mortality. The most convincing data emerged recently from the SOS (Swedish Obese Subjects) study showing reduced long-term cardiovascular mortality following bariatric surgery, largely owing to decreased myocardial infarction risk (7). Although specific mechanisms for cardiovascular benefit remain unknown, plasma insulin appeared to emerge as a primary determinant of cardiac events, providing evidence that insulin resistance may contribute significantly to the pathogenesis of vascular disease in obesity (7).

The vascular endothelium plays a key role in the regulation of arterial tone, blood flow, inflammation, and thrombosis (8,9). Endothelial phenotype serves as a barometer of overall vascular health and displays impairment in insulin-resistant states, and severity of both microvascular and macrovascular dysfunction independently predict future cardiovascular events (8,10–14). The purpose of the study was to determine whether the effects of weight loss on arterial function are differentially modified by insulin status in overweight and obese individuals undergoing weight-reduction intervention.

Methods

Patients. Overweight adult men and women (age $\geq$18 years) with BMI $\geq$25 kg/m^2 seeking weight-loss treatment at the Boston Medical Center Nutrition and Weight Management Clinic (n = 208) were prospectively followed. This hospital-based weight loss intervention program uses a comprehensive approach for obesity management using behavioral, dietary, medical, and/or surgical treatments that are individualized based on clinical and patient decisions.

Interventions comply with established National Heart, Lung and Blood Institute clinical guidelines (15) and included medical therapy with dietary/lifestyle modification (n = 100; 48%) and bariatric surgery (n = 108; 52%). Low-carbohydrate Atkins-type or Mediterranean diets were not specifically prescribed. Nearly all bariatric surgical procedures comprised the Roux-en-Y gastric bypass operation (n = 106); 2 patients underwent laparoscopic adjustable gastric banding. The analyses represent data from patients collected to date from an ongoing prospective cohort study designed to examine vascular responses to weight loss. Patients with unstable medical conditions such as recent coronary syndromes (within 6 months), congestive heart failure, systemic infection, acute illness, malignancy, or pregnancy were excluded. The study was approved by the Boston Medical Center Institutional Review Board, and all patients gave written informed consent.

Vascular function studies. Each patient underwent a forearm brachial artery ultrasound vascular study twice, performed at baseline before lifestyle and/or surgical intervention and follow-up after a median of 11.7 months (interquartile range: 4.6 to 13.0). Vascular studies were performed during a fasting state in a quiet, temperature-controlled room under resting conditions by trained sonographers (16). Brachial vasomotor responses were examined using a noninvasive, standardized method of ultrasound with a Toshiba Powervision 6000 system (Toshiba Medical, Tustin, California). Brachial artery 2-dimensional diameter (mm) images and pulse Doppler flow velocity (cm/s) were measured at the antecubital crease. Brachial flow-mediated dilation (FMD) following a 5-min cuff occlusion in an upper arm position served as a measure of

Abbreviations and Acronyms

BMI = body mass index
FMD = flow-mediated dilation
HbA_{1c} = glycosylated hemoglobin
HDL = high-density lipoprotein
HOMA = homeostasis model assessment
LDL = low-density lipoprotein

Table 1 Baseline Clinical Characteristics Stratified by Plasma Insulin Level

	Lower Insulin≤12 μIU/ml (n = 109)	Higher Insulin>12 μIU/ml (n = 99)	p Value
Age, yrs	44.8 ± 11	44.9 ± 11	0.92
Female, %	85	78	0.16
Race/ethnicity, %			0.49
White	52	58	
African American	30	21	
Hispanic	16	19	
Other	2	2	
Weight, kg	115 ± 26	131 ± 29	<0.0001
BMI, kg/m^2	42 ± 8	47 ± 9	<0.0001
SBP, mm Hg	130 ± 15	129 ± 14	0.81
DBP, mm Hg	74 ± 10	72 ± 10	0.11
Total cholesterol, mg/dl	191 ± 36	186 ± 38	0.37
Triglycerides, mg/dl	89 (67–146)	130 (89–171)	<0.001
LDL-cholesterol, mg/dl	117 ± 31	112 ± 33	0.24
HDL-cholesterol, mg/dl	50 ± 13	45 ± 9	<0.001
Glucose, mg/dl	92 (87–100)	100 (91–116)	0.05
Insulin, μIU/ml	8 (6–10)	19 (14–26)	<0.0001
HOMA	2.0 (1.4–2.4)	4.6 (3.5–6.9)	<0.0001
HbA_{1c}, %	6.0 ± 1.2	6.5 ± 1.5	0.01
Vascular function parameter, %			
Hyperemic flow increase	779 ± 400	666 ± 395	0.04
FMD	9.2 ± 4.5	8.4 ± 4.8	0.23
Comorbidity, %			
Hypercholesterolemia	34	42	0.21
Diabetes mellitus*	21	43	<0.001
Coronary artery disease	4	15	0.01
Hypertension	39	57	0.01
Medical therapy, %			
Antihypertensive	43	59	0.03
Lipid-lowering	19	30	0.06
Hypoglycemic†	17	32	0.01
Insulin	3	8	0.12

Values are mean ± SD, %, or median (interquartile range). *Diabetes mellitus included a medical diagnosis of type 1 or 2 diabetes. One participant in the lower insulin group was diagnosed with type 1 diabetes. †Excluded insulin use.

BMI = body mass index; DBP = diastolic blood pressure; FMD = flow-mediated dilation; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; LDL = low-density lipoprotein; SBP = systolic blood pressure.

endothelium-dependent macrovascular function, expressed as percent change in brachial diameter before and 60 s after cuff occlusion. Brachial artery reactive hyperemia expressed as the percent change in hyperemic forearm blood flow increase after cuff occlusion served as the index measure of endothelium-dependent microvascular function (10,12,17,18).

Clinical and metabolic measures. Clinical characteristics, including blood pressure, height, weight, and BMI, were recorded on the same day as the vascular studies. Weight was measured using a calibrated scale (Ohaus, Pine Brook, New Jersey). Biochemical analyses including lipid, glucose, and insulin levels; homeostasis model assessment of insulin resistance (HOMA); and glycosylated hemoglobin (HbA_{1c}) were quantified from blood samples collected in a fasting state during each visit. Medications were recorded for all visits, including antihypertensive, hypoglycemic, and lipid-lowering regimens.

Statistical analyses. Analyses were completed using SAS for Windows, version 9.1 (SAS Institute Inc., Cary, North Carolina). Data are presented as mean ± SD, median with interquartile range, or proportions (%), unless otherwise indicated. The primary outcome variables were FMD (%) and hyperemic flow increase (%). Absolute change was calculated as the numerical value difference between baseline and follow-up. Histograms and normal probability plots were used to determine whether continuous variables were normally distributed or skewed. Baseline triglyceride, glucose, and insulin levels and HOMA were nonnormally distributed and analyzed following natural log transformation. Informed by data from the SOS study (7), our a priori hypothesis was that the effects of weight loss on vascular function would differ by plasma insulin levels; as such, we stratified our analyses by baseline insulin level. Participants were dichotomized into 2 groups based on median baseline insulin concentration, for which the lower insulin group was defined as ≤12 μIU/ml (n = 109) and higher insulin group >12 μIU/ml (n = 99). In separate models, analysis of covariance (proc GLM in SAS) was used to examine the effect of 5% or 10% weight-loss cut points, based on expert target recommendations for weight reduction in the management of obesity (15) and on changes in vascular and clinical parameters stratified by insulin status. Baseline age and BMI were included as covariates in all models. In addition, models were adjusted for baseline values for the outcome of interest. For example, in analyses examining the effect of 10% weight loss on change in FMD, baseline FMD was included as a covariate. The exposures were treated as dichotomous variables (e.g., ≥10% weight loss or not) and outcomes and covariates as continuous ones. We included interaction terms in models to formally test for effect modification of the association between weight loss and vascular function by baseline insulin status. Medication changes were analyzed across insulin strata and weight-loss categories. All group differences were examined using the Student *t* test, chi-square test, or Fisher exact test as appropriate and within weight-loss group changes by paired Student *t* tests. Partial Pearson correlation adjusted for baseline age and BMI was used to examine the association between changes in clinical data and vascular function parameters. For all analyses, a p value <0.05 was considered statistically significant.

Results

Study population. A total of 208 patients (mean age 45 ± 11 years; 82% female; BMI 45 ± 9 kg/m^2) were enrolled. Nearly all participants were obese, with BMI >30 kg/m^2 (n = 205; 99%). Participants were 55% white, 26% African American, and 17% Hispanic, reflecting demographics of the general population seeking weight-loss treatment in our urban tertiary center. Approximately half (n = 109; 52%) of the participants underwent bariatric surgery, and 48% (n = 99) received lifestyle intervention alone. For the entire group, median follow-up was 11.7 months and mean weight loss 14 ± 14%.

Table 2 Effect of 10% Weight Loss on Clinical Parameters Stratified by Insulin Level

	Lower Insulin ≤12 μIU/ml			Higher Insulin >12 μIU/ml		
	Weight Loss <10% (n = 59)	Weight Loss ≥10% (n = 50)	p Value	Weight Loss <10% (n = 37)	Weight Loss ≥10% (n = 62)	p Value
BMI, kg/m^2	−1.4 (0.5)	−10.3 (0.6)	<0.0001	−0.7 (0.7)	−12.4 (0.5)	<0.0001
SBP, mm Hg	0 (2.1)	−8.4 (2.4)	0.01	−3.2 (2.5)	3 (1.9)	0.06
DBP, mm Hg	−0.8 (1.2)	−1.7 (1.4)	0.65	0.2 (1.5)	2.8 (1.1)	0.17
Total cholesterol, mg/dl	−6.2 (4)	−13.9 (4.2)	0.20	−5.4 (5.2)	−13.7 (3.8)	0.21
Triglycerides, mg/dl	−6.8 (5.9)	−31.7 (6.2)	0.01	−7.3 (10.0)	−35.8 (7.4)	0.03
LDL-cholesterol, mg/dl	−4.3 (3.3)	−12 (3.5)	0.12	−4.2 (4.3)	−10 (3.1)	0.28
HDL-cholesterol, mg/dl	0 (1.5)	3.9 (1.6)	0.10	0.2 (1.9)	3.6 (1.4)	0.16
Glucose, mg/dl	−1.7 (2.7)	−7.3 (2.9)	0.18	13.2 (5.4)	−13.5 (4.1)	<0.001
Insulin, μIU/ml	1.9 (0.9)	−3 (0.9)	<0.001	−2.9 (1.8)	−14.2 (1.4)	<0.0001
HOMA	0.34 (0.21)	−0.82 (0.22)	<0.001	0.10 (0.95)	−4.33 (0.74)	<0.001
HbA_{1c}, %	−0.14 (0.07)	−0.51 (0.07)	<0.001	−0.07 (0.15)	−0.95 (0.11)	<0.0001

Values are mean (SE) adjusted for baseline values for age, BMI, and the outcome of interest. Analysis of covariance was used to determine the difference in change in clinical parameters between dichotomous weight-loss groups.

Abbreviations as in Table 1.

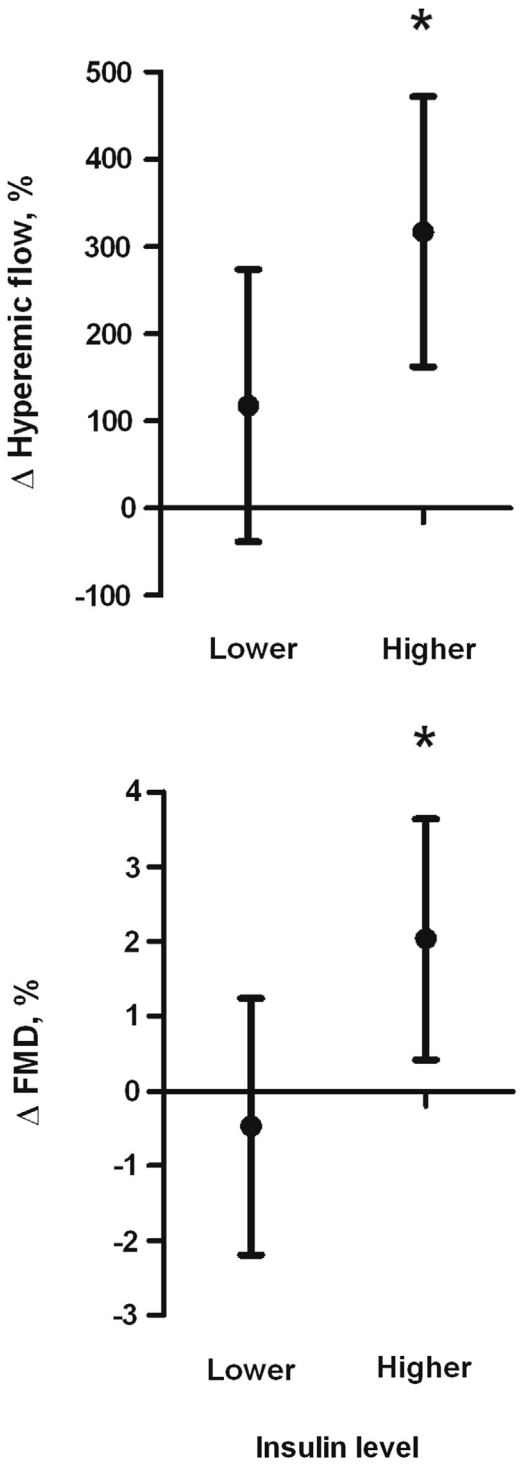

Figure 1 **Effect of ≥10% Weight Loss on Vascular Function**

Brachial artery flow-mediated (FMD) vasodilation and hyperemic flow improved significantly in the baseline higher insulin, but not lower insulin group. Values represent mean (95% confidence interval) difference in change in vascular function between ≥10% versus <10% weight loss, adjusted for baseline age, body mass index, and vascular function. *p < 0.05.

Baseline clinical data stratified by median plasma insulin concentration are displayed in Table 1. Patients in the higher insulin group (>12 μIU/ml) had higher BMI, triglyceride levels, and HOMA and lower high-density lipoprotein (HDL)-cholesterol values ($p < 0.05$). Prevalence of diabetes mellitus, coronary artery disease, hypertension, and medications used to treat these conditions were also higher in this group. Microvascular function as measured by brachial artery hyperemic flow (reactive hyperemia) was lower in the higher insulin group ($p < 0.05$), whereas brachial FMD was comparable between insulin strata.

Weight loss and clinical parameters. As shown in Table 2, ≥10% weight change was associated with a significant decline in BMI, HOMA, HbA_{1c}, and insulin and triglyceride levels in both higher and lower baseline insulin categories ($p < 0.05$ for all). A threshold cut point of 5% weight loss induced similar, but less pronounced, metabolic changes (data not shown). Whereas individuals with higher plasma insulin concentrations achieved improvements in metabolic variables that were directionally similar to those in the lower insulin group, incremental decrease in insulin levels and HOMA among those with ≥10% weight loss was more than 4 times greater in the higher insulin group (−14.2 and −4.3 μIU/ml, respectively) as compared with the lower insulin group (−3.0 and −0.82 μIU/ml, respectively) despite a comparable degree of weight change. The proportion of patients who underwent surgical intervention was similar in lower compared with higher insulin categories (47% vs. 58%; $p = 0.12$). In individuals who lost ≥10% weight ($n = 112$), weight change was similar between lower and higher insulin strata (24.0 ± 10.0% vs. 25.8 ± 10.1%, respectively; $p = 0.34$). However, the majority of patients achieved ≥10% weight loss as a result of bariatric surgical intervention, which did not differ between higher and lower insulin groups (87% vs. 88%; $p = 0.89$).

Weight loss and vascular function. As shown in Figure 1, in models adjusted for baseline age, BMI, and vascular function, ≥10% weight change significantly improved hyperemic blood flow (microvascular function) and FMD (macrovascular function) in patients with higher baseline insulin (both $p < 0.05$), whereas 5% weight change was only associated with improved microvascular responses ($p = 0.02$) (Fig. 2). Although a trend for increased reactive hyperemia was observed ($p = 0.08$), similar degrees of weight loss did not significantly alter microvascular or macrovascular responses in patients with lower baseline insulin levels. The inclusion of change in hyperemic flow increase as a covariate in models predicting change in FMD did not alter these relationships, suggesting that improvement in FMD in the higher insulin strata was not exclusively mediated by changes in flow. Results for ≥10% weight loss and vascular improvement were similar after excluding patients using insulin clinically ($n = 11$) and adjustment for changes in medications, blood pressure, lipids, glucose, HOMA, and HbA_{1c} in analysis of covariance models, thus demonstrating that these parameters did not confound the findings. In

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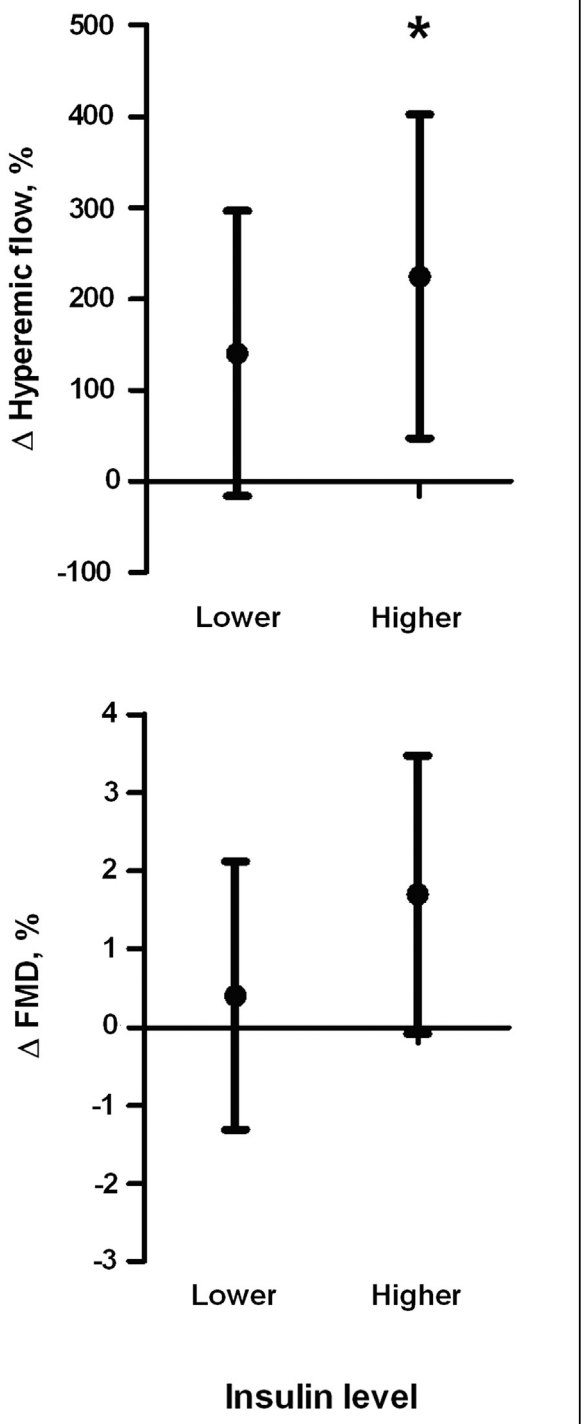

Figure 2 Effect of ≥5% Weight Loss on Vascular Function

Brachial artery hyperemic flow improved significantly only in the baseline higher insulin group. Values represent mean (95% confidence interval) difference in change in vascular function between ≥5% versus <5% weight loss, adjusted for baseline age, body mass index, and vascular function. *p < 0.05. Abbreviation as in Figure 1.

formal tests of interaction, the association between 10% weight loss and change in FMD significantly differed by baseline insulin status (p = 0.04), and there was a suggestion of effect modification with change in hyperemic flow increase set as the dependent variable (p = 0.1).

As metabolic improvements occurred with weight loss, individuals discontinued medications for the treatment of hypertension, dyslipidemia, and glucose intolerance as displayed in Table 3. A ≥10% weight reduction was associated with greater abatement in medication use compared with <10% weight change. There was a strong trend for reduced hypoglycemic drug use following weight loss in the higher versus lower insulin group (p = 0.05); otherwise, there were no significant differences in discontinuation of antihypertensive or lipid-lowering treatment across insulin strata.

Metabolic and vascular effects stratified by weight loss. Individuals who achieved ≥10% weight loss (n = 112) had significantly improved total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, HDL-cholesterol, glucose, and insulin levels and HOMA (p < 0.05 vs. baseline). Compared with participants with <10% weight loss, there were more favorable changes in triglyceride (p = 0.002), HDL-cholesterol (p = 0.04), glucose (p = 0.003), insulin (p < 0.0001) levels, HOMA (p < 0.0001), and HbA_{1c} (p < 0.0001), and trend toward improved LDL-cholesterol (p = 0.06) and total cholesterol (p = 0.09) levels (data not shown). Patients with ≥10% weight loss exhibited 206% (95% CI: 99% to 313%; p = 0.0002) improvement in hyperemic flow increase compared with <10% weight decline, but no group difference in change in FMD was detected (p = 0.25). In analyses adjusted for age and BMI, changes in microvascular function correlated negatively with change in insulin levels (r = −0.19; p = 0.01), HOMA (r = −0.16; p = 0.03), and LDL-cholesterol levels (r = −0.19; p = 0.01), and macrovascular function correlated positively with HDL-cholesterol levels (r = 0.15; p = 0.04).

Discussion

In a cohort of obese patients undergoing weight-reduction therapy, baseline insulin status was a key determinant of the positive effects of weight loss on vascular function, with higher-risk hyperinsulinemic patients deriving the greatest benefit. A modest 5% decrease in body weight improved cardiovascular risk factors and microvascular function in patients with higher insulin levels, and weight reduction of ≥10% reversed metabolic dysfunction to a greater extent and improved both microvascular and macrovascular vasodilator responses. Given the key role of vascular homeostasis in mitigating cardiovascular risk, our findings suggest that reversal of insulin resistance and endothelial dysfunction may be mechanistically intertwined and represent important therapeutic targets in obesity.

Few studies have examined the relationship between intentional weight loss and cardiovascular mortality. A 12-year observational study in overweight women reported that weight change with lifestyle modification reduced mortality, with greatest impact in high-comorbidity subsets (19). Similarly, retrospective analysis of bariatric surgical patients

Table 3 Medication Discontinuation Following Weight Loss Across Treatment Classes Stratified by Insulin Status

	Lower Insulin ≤12 μIU/ml		
Weight Loss	<10%, n = 59	≥10%, n = 50	p Value
Antihypertensive	10 (6)	26 (13)	0.03
Lipid-lowering	0 (0)	20 (10)	0.0002
Hypoglycemic	2 (1)	20 (10)	0.002
	Higher Insulin >12 μIU/ml		
Weight Loss	<10%, n = 37	≥10%, n = 62	p Value
Antihypertensive	3 (1)	37 (23)	<0.0001
Lipid-lowering	3 (1)	21 (13)	0.01
Hypoglycemic	0 (0)	36 (22)	<0.0001

Values are % discontinuation (n).

showed improved cardiovascular survival during a 7.1-year follow-up period (20). The strongest evidence to date comes from the prospective SOS study, which recently reported 15-year follow-up data demonstrating nearly 30% reduction in long-term risk of myocardial infarction and stroke with bariatric weight loss (7,21). Surprisingly, although neither BMI nor improvement in many traditional risk factors were linked to cardiovascular benefit, secondary analyses identified baseline plasma insulin levels as the primary determinant of cardiovascular risk. Our results build upon this observation because the notion that insulin status stratifies vascular improvement was evident from our study, prompting recognition that the reduced number of cardiovascular events following weight loss may be tied to mechanisms of improved insulin sensitivity and arterial homeostasis.

Although prior small studies showed that vascular function improved with weight decline, differential associations by insulin status have not been specifically explored (22–25). Circulating asymmetrical dimethylarginine levels, an endogenous endothelial nitric oxide synthase inhibitor, decline preferentially in insulin-resistant patients following weight loss (26). We similarly observed that vascular benefits of weight reduction were primarily manifest in hyperinsulinemic patients. From a clinical perspective, several important points can be emphasized from our study. First, baseline differences in insulin status did not appear to modulate extent of weight loss achieved. Second, it was evident that not all obese individuals gained equal metabolic or vascular benefit from weight reduction. Third, vascular improvement did not appear to be confounded by medication changes that were similar across insulin strata. Fourth, our data provide a potential mechanism for the SOS study findings that confine the effectiveness of weight loss in reducing cardiac events to high insulin categories. Lastly, our results also suggest that ≥10% weight change may be required for integrated improvement in microvascular and macrovascular functions, which further supports National Heart, Lung and Blood Institute recommendations targeting 10% weight reduction for medical benefits (15).

Elevated circulating insulin levels likely reflect a pathophysiological state of systemic insulin resistance that is associated with vascular endothelial dysfunction, arterial inflammation, oxidative stress, and accelerated atherosclerosis (27–31). The magnitude of insulin resistance varies widely among obese individuals, and higher insulin concentrations are linked to dysfunctional vascular phenotypes in both coronary and peripheral circulations (32,33). Animal and human data show that pathological abnormalities involve defects in vascular insulin signaling, such as the insulin receptor substrate 1/phosphoinositide 3-kinase/Akt pathway associated with impaired endothelial nitric oxide synthase activity and nitric oxide bioaction, and expression of proinflammatory, prothrombotic, and vasoconstrictive mediators that support a proatherogenic vascular phenotype (30). These abnormalities manifest, in part, as defects in both microvascular and macrovascular endothelial function that have been prospectively and independently linked to adverse cardiovascular events such as myocardial infarction and stroke (10,12,34,35).

Although our results expand our understanding of the complex relationship among obesity, insulin resistance, and arterial disease, further questions remain. Evidence is mounting that bariatric surgery is more effective than conventional treatment for durable weight loss and diabetes remission (36,37). As expected, bariatric intervention was more effective in achieving rapid and more extensive weight loss during the follow-up period (≈1 year) compared with conventional therapy in our cohort. Although our study was not designed to compare weight intervention methods, the proportion of individuals treated surgically was the same across insulin strata, suggesting that vascular benefits were not a consequence of differential operative intervention. In that regard, recent findings from the Look AHEAD (Action for Health in Diabetes) study reported that although intensive lifestyle modification through diet and exercise induced 6% weight loss at 9.6 years with positive health benefits, the number of cardiovascular events was not lowered (38). In addition, several dietary intervention studies in which mean weight loss was <10% reported no significant macrovascular improvement (39,40). This adds further debate, not only to the search for optimal weight-loss strategy, but also regarding the minimal amount of weight change required to elicit comprehensive health benefits.

Because the most important health risk of obesity is the development of cardiovascular disease, the clinical

implication that insulin resistance and vascular dysfunction drive, in part, the association between obesity and cardiovascular risk raises issues regarding treatment strategies. As such, pharmacological therapies for insulin sensitization have displayed variable cardiovascular effects (41–43). Enhanced insulin sensitivity achieved by weight loss likely involves additional complex beneficial mechanisms mediated by modulation of fat tissue phenotypes, reduction of adipose-derived inflammatory cytokines, fatty acid mobilization, and hormonal shifts (23,44–46). In our cohort, changes in microvascular function were more sensitive to weight modification, and insulin resistance correlated more closely with microvascular responses than conduit vessel function. How specific therapeutic strategies intertwine with favorable modification of vascular phenotypes is clinically important and warrants further investigation.

Study limitations. The present study has several limitations. First, the study was not randomized, although interventions were based on clinical decisions that likely reflect quotidian practice. Despite its observational nature, the prospective design maintained temporal relationship between alterations in metabolic parameters and vascular function during the follow-up period. Second, the study did not examine cardiac outcome data, which limits generalization regarding absolute risk. We recognize that forearm hyperemia represents a complex physiological response that is only partly endothelium dependent. However, our endpoints of arterial function as surrogates of cardiovascular risk have been prospectively validated in multiple outcomes studies (11). Third, we used an arbitrary cutoff (median split) to categorize our participants into higher and lower baseline insulin categories. Insulin values of our sample of severely obese participants were elevated compared with normal levels reported in community-based studies (47). Additional studies with large sample sizes and conducted in obese populations are needed to explore alternative plasma insulin cutoffs that may maximize the differential relationships observed in our study. Lastly, sustainability of relatively short-term (~1 year) vascular changes in our cohort has not been examined in the long-term and requires continued investigation.

Conclusions

Our results suggest that reduction of cardiovascular risk in obesity may vary as a function of reversing insulin resistance and vascular endothelial dysfunction. Although we emphasize that intentional weight loss of any kind averts a multitude of health risks associated with excess adiposity, our data suggest that attempts to reduce cardiovascular risk by weight reduction should be particularly emphasized in obese hyperinsulinemic individuals.

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Key Words: bariatric surgery ■ hyperinsulinemia ■ obesity ■ vasculature ■ weight loss.

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