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Obesity, Weight Loss, and Vascular Function

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Obesity promotes the development of several major cardiovascular risk factors. Moreover, excess adiposity may play a direct role in initiating atherosclerosis as fat cells are capable of affecting the systemic vasculature through a variety of mechanisms. Recent studies demonstrate that obesity *per se* may impair vascular endothelial function. This is important as endothelial dysfunction is a key factor in the pathogenesis of atherosclerosis and in triggering acute ischemic events. At present, few studies have determined the beneficial impact of weight loss on cardiovascular outcomes and mortality. However, several experiments have demonstrated that weight loss can lead to improvements in endothelial function, a validated surrogate marker of cardiovascular risk. The mechanisms whereby weight loss restores vascular health are likely multifactorial. However, the relative importance of reduced adiposity versus the specific dietary regimens prescribed, the role of concomitant exercise, and the direct effect of medications remain unclear. Several other unresolved issues such as the longevity of improvement, the amount of weight loss required, and whether the improvement in endothelial function actually translates into a reduction in cardiovascular events also remain to be determined. Nevertheless, lifestyle changes that lead to weight reduction are able to improve vascular function in overweight adults.

Key Words: Endothelium; obesity; vascular function; cardiovascular risk.

Introduction

Obesity increases the risk for developing hypertension, dyslipidemia, and insulin resistance *(1)*. Abdominal adiposity is central in the pathogenesis of the clustering of cardiovascular (CV) risk factors termed the metabolic syndrome *(2)*. It is therefore not surprising that both an increased body mass index and abdominal adiposity are associated with enhanced long-term CV risk *(3)*. Moreover, some studies imply that excess adiposity may in-itself be an atherosclerosis risk factor *(1)*. Unfortunately, there is a burgeoning growth of obesity within the United States. Given its role in CV disease, some estimates suggest that this epidemic will lead to a future reduction in life expectancy *(4)*. With this in mind, it is important to understand the mechanisms whereby obesity promotes CV disease as well as the effect that weight loss has on clinical outcomes and in altering CV physiology *(1,2)*.

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Mechanisms of Obesity-Related Vascular Dysfunction

Obesity has the potential to negatively impact CV health through a wide variety of mechanisms *(1,2)*. One important pathway is via impaired arterial vascular function. Obesity, insulin resistance, and the metabolic syndrome are all associated with vascular endothelial dysfunction and reduced arterial compliance *(1,5,6)*. Obesity is capable of both directly and indirectly (via altering conventional risk factors) affecting the systemic vasculature (Fig. 1). Excess adiposity *per se*, even in the absence of associated risk factors, has been associated with reduced endothelial function *(7–9)*. Enhanced oxidative stress and inflammatory cytokines appear to be central in the pathophysiology. In addition, resistance to the vasomotor function of insulin and leptin, activation of the renin–angiotensin–aldosterone system, and direct effects of several adipokines have all been implicated *(5–9)*. The mechanisms underlying this linkage have recently been described in detail *(5,6)*. Therefore, this brief review will focus on the evidence that weight loss can improve vascular health and the implications that can be drawn from critically analyzing the studies published to date.

The association between obesity and endothelial dysfunction is crucial because the latter is pivotal in the pathogenesis of atherosclerosis and in the triggering of acute CV events *(10)*. The arterial endothelium is most commonly noted for the regulation of vascular tone by releasing a wide variety of vasoactive molecules (e.g., nitric oxide, endothelin). However, it also plays a central role in modulating thrombosis/coagulation, inflammation, oxidative stress, cell growth, and angiogenesis *(10,11)*. By investigating aspects of the relationship between obesity and vascular function, the mechanisms whereby adiposity impacts CV health can be elucidated. In addition, endothelial dysfunction is a validated surrogate marker of CV health. Few clinical trials have shown that weight loss reduces CV disease (e.g., myocardial infarctions) *(12)*. On the contrary, a growing body of studies has demonstrated that impaired arterial function

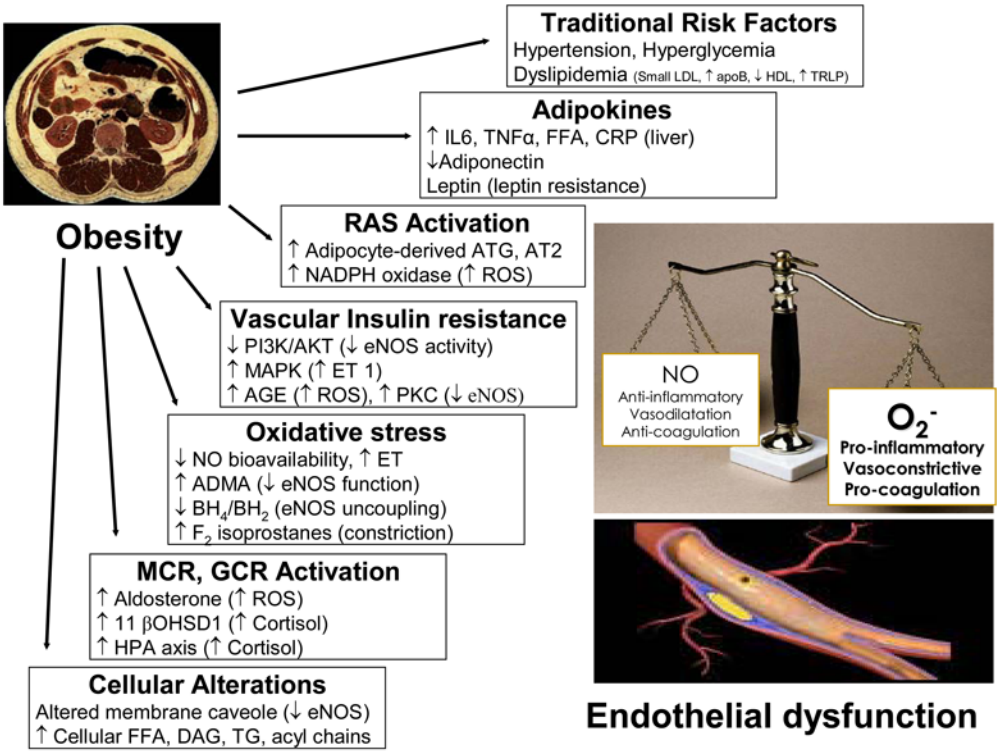

Fig. 1. Mechanisms linking obesity to vascular endothelial dysfunction. (TRLP, triglyceride rich lipoproteins; IL6, interleukin-6; TNFα, tumor necrosis factor alpha; FFA, free fatty acids; CRP, C-reactive protein; ATG, angiotensinogen; AT2, angiotensin 2; ROS, reactive oxygen species, PI3K/AKT, Phosphotidylinositol 3 kinase–protein kinase B pathway; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase; ET-1, endothelin 1; AGE, advanced glycation endproducts; PKC, protein kinase C; NO, nitric oxide; ADMA, asymmetric dimethyl arginine; 11βOHSD1, 11 beta hydoxy steroid dehydrogenase-1; HPA axis, hypothalamic pituitary adrenal axis; DAG, diacyl glycerol; TG, triglycerides.)

is independently predictive of adverse CV outcomes *(10,11)*. Therefore, restoration of endothelial function by weight loss (and possibly in combination with other modalities) conveys important independent positive prognostic information.

Weight Loss and Endothelial Function

Several clinical trials have investigated the effect of short-term weight loss on vascular endothelial function (Table 1) *(13–24)*. It is important to note that all trials, except one *(15)*, have been of very short duration (≤6 mo). In addition, there is a great deal of heterogeneity among studies in regards to the techniques to assess "endothelial function," the specific dietary regimens and nutritional components prescribed, the usage of medications and/or surgery, and, most importantly, concomitant exercise training. Despite these differences, 11 of the 12 studies reported an improvement in "endothelial function" (Table 1). Therefore, the most important conclusion that can be drawn from the available evidence is that comprehensive therapeutic lifestyle changes (e.g., diet, exercise) that lead to weight loss are capable of rapidly producing meaningful improvements in vascular health. This provides plausible support to the notion that lifestyle changes leading to reductions in body weight will positively affect CV outcomes. These trials, however, do not conclusively demonstrate that weight loss in-and-of-itself improves vascular function. Too little data are available to make firm conclusions in this latter regard. However, this limitation should not lessen the importance of the fact that lifestyle changes leading to weight loss can restore obesity-related endothelial dysfunction. It is simply that the specific aspect(s) of the combined lifestyle changes (e.g., weight loss, exercise, diets) principally responsible remain to be determined.

Does weight loss itself directly improve endothelial function? To address this issue, further scrutiny of the trials is required. First, only 5 *(15,17,19,21,22)* of the 12 studies enrolled purely "healthy" overweight patients without any other coexisting obesity-related morbidities. Several of the trials enrolled obese/overweight adults with a significant proportion of patients having various co-morbidities (e.g., hypertension, diabetes) *(13,18,20,23,24)*. Two other trials enrolled only patients with a history of gestational diabetes *(16)* and hypertension *(14)*. Therefore, less than half of the published studies can provide direct information regarding the impact of weight loss on the vascular dysfunction resulting solely from obesity itself (obesity-related endothelial dysfunction). In the other studies, the lifestyle changes and weight loss may improve endothelial function, which is important in-itself. However, it is not clear if this improve-

Table 1
Trials of Weight Loss and Biomarkers of Vascular Function

Study	Subject	BMI (kg/m^2)	Δ BMI (kg/m^2)	Δ wt (kg)	Intervention	Results	Results related to Δ wt
Ferri (1999) *(13)*	22 HTN 19 nL BP	33.2 32.9	–2.6	—	Total of 800 kcal/d for 12 wk	↓ circulating markers of endothelial activation (VCAM-1, ICAM-1, E-selectin, vWF)	No (Yes: only for E-selectin change)
Sasaki (2002) *(14)*	11 HTN	27.7–36.7	—	–4.3	Total of 800 kcal/d for 2 wk	Enhanced forearm blood flow response to acetyl choline intra-arterial infusion	No
Ziccardi (2002) *(15)*	56 Women	37.2	–4.7	–9.8	Total of 1300 kcal/d + exercise ± liposuction for 1 yr	Improved blood pressure response to L-arginine injection, ↓ VCAM-1, ICAM-1, P-selectin (↓ blood pressure response correlated to weight loss)	Yes
Bergholm (2003) *(16)*	24 Women 23 Women	32.3 32.3	–2.7 –2.7	–7.4 –7.3	Hypocaloric diet for 3–6 mo vs diet + orlistat for 3–6 mo	Enhanced forearm blood flow response to acetyl choline infusion in orlistat group only (correlated *only* to ↓ LDL-C by orlistat)	No
Sciacqua (2003) *(17)*	28	33.1	–5.6	–12.5	↓ 6–800 kcal/d + exercise for 14–16 wk	Enhanced forearm blood flow response to acetyl choline infusion (correlated *only* to improved insulin sensitivity)	No (after accounting for change in insulin sensitivity)
Hamdy (2003) *(18)*	24 IRS	36.7	–2.7	–7.4	↓ 500 kcal/d + exercise for 6 mo	Improved brachial flow-mediated dilatation (correlated to weight loss). No microvascular improvement in function	Yes
Brook (2004) *(19)*	43 Healthy	34.9	–2.3	–6.5	↓ 500 kcal/d + orlistat for 3 mo	No change in brachial flow-mediated dilatation	No
Raitakari (2004) *(20)*	67	35.2	–3.8	–11	Total of 580 kcal/d for 6 wk	Improved brachial flow-mediated dilatation (correlated *only* to ↓ glucose)	No
Woo (2004) *(21)*	42 Children 41 Children	24.5 25.4	-0.4 –0.1	+0.6 +0.6	900–1200 kcal/d for 6 wk vs diet + exercise for 6 wk	Improved brachial flow-mediated dilatation in both groups, although significantly greater increase with diet + exercise	No
Ribeiro (2005) *(22)*	18 Children 21 Children	30 28	–3 –3	–5 –7	1400 kcal/d for 16 wk vs diet + exercise for 16 wk	Forearm vascular conductance improves during handgrip exercise and mental stress in diet + exercise group only (not in diet alone group)	No
Vazquez (2005) *(23)*	26	46.2	–9.5	–26.7	4.2 mo after bariatric surgery	Improved hand vein response to bradykinin, ↓ E-selectin, P-selectin, PAI-1, vWF	No
Gokce (2005) *(24)*	17 24	42 50	–4 –13	–11 –35	Diet, exercise encouraged vs above + bariatric surgery	Flow-mediated dilatation improved in both groups but significantly more in the surgery group (correlated *only* to glucose reduction).	No

ment is related to the vascular dysfunction resulting from obesity or from the co-morbidities. This issue is not trivial. If weight loss is not beneficial to the vasculature in lone obesity, but is helpful in overweight patients with co-morbidities (e.g., hypertension, diabetes), then it is rationale to assume that therapeutic lifestyle changes would have more positive clinical impacts in the latter group of patients.

In addition, six studies included significant exercise training as part of the weight loss regimen in at least a portion of the subjects (Table 1) *(15,17,18,21,22,24)*. Exercise is well-known to directly improve vascular endothelial function in a variety of disease states and in healthy people *(25)*. Thus, in half of the available studies it remains entirely unclear if the weight loss or the exercise is principally responsible for the favorable outcomes. In fact, in the study by Ribeiro et al. only the diet plus exercise regimen was capable of restoring the obesity-related endothelial dysfunction *(22)*. A similar degree of weight loss by diet alone was not successful. In the study by Woo et al., endothelial function improved with diet and weight loss (no exercise). How-

ever, patients who also exercised had significantly greater improvements compared to those who lost weight by diet alone *(21)*. These studies provide evidence that exercise may be an important component (and possibly more potent than weight loss) of the therapeutic lifestyle changes responsible for increasing endothelial function.

To date, we have published the only weight loss study that enrolled solely healthy overweight patients (no co-morbidities) and did not include exercise therapy *(19)*. Our results give the best indication of what weight loss *per se* does to the vascular endothelium of obese patients (Table 1). In other words, does weight loss restore the endothelial dysfunction due entirely to excess adiposity? Forty-three otherwise healthy overweight adults underwent dietary therapy + orlistat 120 mg po QAC for 12 wk. A mean weight loss of 6.5 kg (6.6% of body weight) resulted in very significant reductions in insulin sensitivity, dyslipidemia, and a trend toward reduced C-reactive protein levels. Despite the clear metabolic benefits of weight loss due to diet + orlistat, brachial flow-mediated dilatation (FMD) (endothelial function), arterial compliance, and levels of asymmetric dimethyl arginine did not improve. The amount of weight reduction was very similar to other studies (Table 1), making inadequate weight loss an unlikely explanation for our negative findings. The usage of orlistat is not responsible, as the study by Bergholm et al. found improvements in the diet + orlistat group only *(16)*. We cannot exclude the possibility that the lack of exercise and the specific diet prescription in our trial may have played a role. However, we found a strong independent negative correlation between the reduction in plasma leptin concentration and a worsened brachial FMD following weight loss. We speculated that a reduction in the normal physiological functions of leptin, which mediates an endothelial-dependent vasodilatation *(26, 27)*, may have blunted the metabolic benefits of weight loss upon the vasculature.

Can a reduction of the direct vascular effects of leptin on endothelial function explain our findings? Although plausible, leptin was most likely reduced in the other positive weight loss trials as well. One possible explanation for our discordant findings may be the initial degree (pre-weight loss) of arterial sensitivity to the vasomotor functions of leptin. It is conceivable that the overweight patients in other positive studies were more "leptin resistant" as a consequence of their less healthy status (e.g., more severe obesity, presence of obesity-related co-morbidities) *(28)*. If patients in our study of lone obesity retained some initial vascular leptin sensitivity, then the reduction in leptin concentrations induced by weight loss could conceivably counter the other metabolic benefits upon the vasculature. If less healthy overweight patients were less vascular sensitive to leptin (similar to the vascular effects of insulin) *(28)*, then weight loss may restore endothelial function without dampening the direct effects of a reduction in leptin. In conjunction, the reduction in visceral obesity would in theory enhance their sensitivity to leptin, thus further improving their endothelial function. Moreover, the improvements in other traditional risk factors (lipids, blood pressure) are also likely to be more robust following weight loss in initially less healthy obese patients. This would further contribute to the restoration of endothelial function. This hypothesis suggests that less healthy obese patients, particularly those with insulin and leptin resistance, stand to gain greater improvements in vascular function following weight loss.

Another important distinction among the studies is the dietary portfolio. Just as with exercise, direct vascular effects of the nutrient components within different diets may be equally (or more) effective in altering vascular function as weight loss. At least two studies have demonstrated that a Mediterranean-type diet is capable of enhancing endothelial function independent of any changes in exercise or weight *(29,30)*. In addition, a low-fat diet can also improve vascular function *(29,31)*. On the contrary, enhanced postprandial lipemia and glycemia can both produce rapid reductions in endothelial function *(32,33)*. This adds to the confusion regarding the weight loss studies (Table 1). It is very possible that alterations in the components of the diets used to achieve weight loss may have had significant direct vascular effects independent of changes in body composition. In particular, the studies that used extreme calorie restriction also tended to produce very positive results in a very rapid fashion. An impact of drastic reductions in energy intake per se cannot thus be excluded.

It should also be noted that the modality used to assess "endothelial function" is important *(10,11)*. Typically, the vasodilatory response to a nitric oxide endothelial-dependent vasoactive mediator such as shear stress (flow-mediated) or receptor activation (acetyl choline) is quantified. The vasoactive portion of endothelial function is thought to parallel the other aspects. However, it is entirely possible that there may be discordant responses among the various modalities utilized and among differing vascular territories observed. The microvascular responses (assessed by blood flow increase to receptor activation) may differ from the conduit artery responses evaluated by brachial or radial FMD. Coronary vessel responses may not perfectly match the peripheral vasculature. Vasodilatory responses may not reflect changes seen in endothelial activation and receptor expression (e.g., soluble VCAM-1). Therefore, it is not surprising if different results are found using the various tools to investigate vascular function, even if all else is kept constant.

It is readily apparent from reviewing the available studies that the improvements in vascular dysfunction do not correlate with the amount of weight loss within the vast majority of the individual trials (Table 1). In fact, a clear relationship between the degree of weight loss and improvement in endothelial function was reported in only 2 of the 12 trials. This further suggests that other aspects beyond weight loss *per se* are important in mediating any improvement in the vascular health of overweight patients. In several of the positive

studies, improvements in glucose and/or insulin sensitivity were correlated with changes in vascular function *(17,20, 24)*. In another, the amount of LDL-C reduction was important *(16)*. This suggests that in order for weight loss to impact the vasculature, substantial changes in the traditional risk factors need to be produced. This is surprising given the fact that obesity *per se* is capable of directly impairing vascular function by a multitude of mechanisms (Fig. 1). An alternative explanation is simply that the trials performed to date have all been too small and underpowered in order to show a direct correlation between weight change and blood vessel function.

Conclusions

A comprehensive prescription of diet (low-fat or Mediterranean), exercise, and weight loss (even when using medications such as orlistat) can improve vascular function within weeks to months in overweight patients. It appears that the benefits are more robust in initially less healthy individuals and in those that undergo concomitant exercise. The relationship between aspects of obesity and vascular function is important for understanding the mechanisms whereby excess adiposity triggers CV disease. Equally important, it suggests that lifestyle changes that lead to weight loss are important modalities capable of improving CV outcomes among obese patients and those with the metabolic syndrome. This latter conclusion is based on the fact that endothelial function is a validated surrogate marker of CV prognosis. Further studies are still required in order to determine several remaining questions. In particular, the importance of the weight loss (or degree of reduction in adiposity) versus other aspects such as the diet prescribed and exercise regimen are unclear. Finally, the duration of benefit upon the vasculature and whether this improvement actually translates into a better long-term CV prognosis remain to be determined. Nevertheless, the over-arching finding of this review strongly supports the beneficial role of lifestyle changes that include diet, exercise, and weight loss in obese patients in order to improve their CV health.

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