Weight Loss and Endothelial Function in Obesity

Endothelial dysfunction, a pathologic feature of obesity, predicts the occurrence of cardiovascular disease (1,2), and is felt to mediate the increased cardiovascular risk associated with a number of classical and nonclassical risk factors. However, the pathogenesis of endothelial dysfunction in obesity remains uncertain. In this field, the major questions center on the relative roles of insulin resistance, fatty acids, or adipocyte-associated cytokines on endothelial function. For example, a number of groups have demonstrated the ability of acute increases in circulating nonesterified fatty acids to induce insulin resistance at both the cellular and whole-body levels (3,4). The observation that such interventions also induce vascular dysfunction (5) has hinted at the mechanism of obesity-associated endothelial dysfunction, but many questions remain.

We are beginning to see studies of the effects of weight loss, achieved through a variety of means, on endothelial function in obesity. These studies are welcome for two reasons: information regarding further benefits of weight loss can help support arguments for better funding, access, and support of weight loss programs by various payors; also, there is a clear opportunity for such studies to contribute materially to our understanding of the pathogenesis of endothelial dysfunction in obesity. Weight loss is generally associated with beneficial changes in variables associated independently with endothelial dysfunction, such as blood pressure and HDL cholesterol, and such studies can therefore provide clues to the pathogenesis of endothelial dysfunction in this setting. This is something of a minefield, however, because the therapeutic lifestyle interventions usually recommended to achieve weight loss include exercise, a confounder that has well-recognized effects on endothelial function. Conversely, pharmacologically assisted weight loss must account for possible direct effects of the medication on endothelial function independent of its effects on weight loss, as well as for potential metabolic and other effects of the medication to improve endothelial function independent of weight loss.

As presented in this issue of Diabetes Care, Bergholm et al. (6) have undertaken a study of the effects of modest weight loss on endothelial function in obese women with a history of gestational diabetes. Subjects were randomly assigned to dietary intervention plus orlistat, or dietary intervention plus matched placebo. The primary end point was the effect of treatment on forearm vascular function, assessed using plethysmography and direct intra-arterial infusion of endothelium-dependent and endothelium-independent vasodilators. Both groups achieved comparable reductions in body weight (~8%), with matched reductions in other anthropomorphic measures and in circulating fasting insulin levels. The timing to achieve target weight loss did not differ between groups, and a weight maintenance diet was instituted for 2–4 weeks in advance of the post-therapy measurements. Changes in circulating lipid levels were matched with two exceptions: the placebo group, but not the orlistat-treated group, had a modest reduction in triglyceride levels, and orlistat, but not placebo, was associated with a significant (but modest) reduction in LDL cholesterol.

The primary analysis of forearm blood flow responses, expressed as a ratio of simultaneously measured blood flow in the treated versus the contralateral arm, revealed improvements in endothelium-independent responses as well as endothelium-dependent responses in the diet+orlistat group, while no effect on endothelium-dependent responses was evident in the diet+placebo group. An alternative analysis is also presented, correcting the blood flow responses in the treated arm for the changes in composition, and not including the data from the contralateral arm. In this analysis, there was no significant change in either group in endothelium-independent responses but a significant improvement in endothelium-dependent responses in the diet+orlistat group only. Subsequent correlational analyses revealed a significant relationship of both endothelium-dependent and -independent blood flow responses with the change in LDL cholesterol concentrations. The authors interpret these findings as an improvement in endothelial function in the diet+orlistat group, with a suggestion that alterations in circulating LDL levels mediate this beneficial effect, rather than another effect of weight loss alone. The finding of apparent changes in control measures of endothelium-independent responses somewhat mitigates the strength of this finding. However, a difference between groups was evident using both analyses and this degree of weight loss alone was insufficient to improve forearm endothelial function. A relationship of LDL cholesterol to vascular function was demonstrated, but unfortunately in this instance, this is not specific to the endothelium-dependent responses. In all, these data put forward the possibility that modest weight loss alone might be insufficient to correct endothelial dysfunction in obesity, but rather that correction of other features of obesity-associated endothelial dysfunction may be required. Although confirmatory studies are needed, this important finding speaks to the mechanism of endothelial dysfunction in obesity.

Relatively few comparable studies exist in the literature to date. Direct measures of the effects of weight loss on endothelial function have been reported by Sasaki et al. (7), who reported improved endothelium-dependent vasodilation with the use of a very low-calorie diet for 2 weeks in obese hypertensive subjects. Circulating markers of endothelial activation have been reported to be improved in obese subjects following 12 weeks of caloric restriction (800 kcal/day), achieving ~9% weight loss (8). Circulating levels of inflammatory cytokines were similarly reduced in obese women following a 1-year multidisciplinary weight loss program.
which achieved at least 10% reduction in weight (9). Although a direct effect of weight loss achieved with d-fenfluramine on ex vivo endothelial function has been reported in aged Sprague-Dawley rats, it is unclear whether this observation reflects an effect of weight loss or a direct effect of the agent used (10). In sum, the available literature suggests beneficial effects of weight loss on a number of axes related to vascular function. Further studies exploring the salient features of the interventions, including the degree of weight loss achieved and the timing of vascular measures in relation to the restoration of eucaloric diet, will be needed to better understand the interactions of obesity and endothelial function.

An important unanswered question is whether more significant weight loss, such as that reported by Zaccardi et al. (9), might itself produce improvements in vascular function. It is possible that the modest weight loss reported in the present study did not attain a critical threshold in correcting the underlying metabolic state as it impacts the vasculature. For example, insulin resistance was not formally measured in the present study. Both groups exhibited an ~30% reduction in circulating insulin levels, but this simple measure might obscure a subtle difference in the alteration in metabolic state between the groups (owing, presumably, to the drug), which itself contributed to the observed effects on vascular function. Similarly, a number of unmeasured but potentially relevant factors can be put forward that might have contributed to the beneficial effect on endothelial function. These could include other metabolic variables such as free fatty acids or homocysteine, measures of oxidative state, adipocyte products such as TNF-α, leptin, or adiponectin, or measures of systemic inflammation such as C-reactive protein. In this context, the observed correlation of the vascular effect with change in LDL cholesterol is of interest, but far from conclusive. These issues notwithstanding, the present study suggests that modest weight loss alone does not sufficiently correct the mechanism by which obesity impacts vascular function.

The relationship of endothelial function measurements such as those applied by Bergholm et al. with cardiovascular event rates remains an area of active investigation. An intriguing possibility is that these measures alone may prove useful in defining the adequacy of therapeutic interventions targeting cardiovascular risk reduction. In this light, the observed failure of modest weight loss alone to improve endothelial function might imply that more aggressive intervention is required to reduce ultimate cardiovascular risk. Measurements of endothelial function may help us better define a sufficient response to any therapeutic intervention in obesity.

In summary, the present study found that modest weight loss alone failed to improve endothelial function in obesity, while weight loss plus orlistat improved vascular function, at least in part by improving endothelium-dependent vasodilation. This latter effect was statistically correlated with an improvement in LDL cholesterol, suggesting that the effects of this classical risk factor on endothelial function in obesity dominated other more direct effects of obesity such as insulin resistance. Further studies will be needed to confirm this group’s findings, and to extend the study of the metabolic effects of weight loss to include other classical and nonclassical variables with potential impact on vascular function. Such studies will both extend our understanding of the pathogenesis of obesity-associated endothelial dysfunction and support therapeutic decision-making that includes among its targets a reduction in adverse cardiovascular outcomes.

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References