Obesity has emerged recently as a major epidemic and is turning out to be a key driving force for the rapid escalation not just in the rates of type 2 diabetes mellitus, but of cardiovascular disease as well. It is estimated that currently \( \leq 300\,000 \) deaths per year are attributable to obesity\(^1\) in the United States, with a significant proportion being attributable to cardiovascular events.\(^2\) It is known that, in morbidly obese subjects, weight loss by bariatric surgery is associated with a reduction in cardiovascular events. However, there is scant evidence for reduction in cardiovascular events related to weight loss in lower risk overweight and obese subjects.

Endothelial function is impaired in obesity,\(^3\) and impaired endothelial function has, in turn, been associated with increased cardiovascular events.\(^4,5\) Thus, it is reasonable to hypothesize that weight loss should be associated with an improvement in endothelial function and, thereby, a decrease in cardiovascular events. In the current issue of Hypertension, Pierce et al\(^6\) report the results of testing the first part of this hypothesis. They describe the effect of weight loss on vascular function as measured by flow-mediated dilation in the forearm and changes in forearm blood flow in response to intraarterial infusions of acetylcholine, an endothelium-dependent vasodilator, as well as sodium nitroprusside, an endothelium-independent vasodilator. In addition, they looked for predictors of changes in vascular function associated with weight loss.

The authors should be commended for undertaking and completing a challenging study with multiple complexities ranging from patient retention to ensuring patient adherence to the prescribed diet and to catheterization of the brachial artery. It is particularly noteworthy that the investigators were able to achieve such a rapid rate of weight loss in the study participants; however, it should be pointed out this rate of weight loss was more aggressive than the \( \approx 10\% \) weight loss over 6 months that is in keeping with the current National Institutes of Health recommendations.

Pierce et al\(^6\) showed that both measures of endothelial function, flow-mediated dilation and changes in forearm blood flow, improved significantly after weight reduction. In addition, they showed that the improvement in forearm blood flow response to acetylcholine was abrogated by methyl-L-arginine, which supports the conclusion that endothelial NO production is increased after weight loss. The results of this study are highly encouraging for obese patients who are attempting to lose weight by dietary means with or without exercise, as well as for the health care professionals who motivate and supervise these patients. These results indicate that endothelial dysfunction is at least partially reversible by weight loss. However, the absence of a lean control group precludes determination as to whether the improvement in vascular reponsivity associated with this degree of weight loss is sufficient to restore normal endothelial function.

Although the positive results of this study are very encouraging, there are a number of questions in the field of obesity-related cardiovascular risk that are yet to be answered.

First, is there a threshold for the magnitude of weight loss at which there is an improvement in vascular function? Weight loss and reduction of fat mass achieved in this study were exceptionally robust, as well as rapid. Clearly, this is a self-selected group, and this magnitude of weight loss over such a brief period is beyond what is achievable in most settings. Most, but not all,\(^7\) reports of improvement in endothelial function associated with weight reduction suggest that weight loss of \( \approx 10\%\)^\(^8,9\) may be required before an improvement in endothelial function can be detected.

Second, is there is a threshold for the duration of weight loss necessary for an improvement in vascular function? In other words, it is still unclear whether there is a minimum duration of weight loss that is required to observe a change in vascular function.

Third, does the weight loss have to be as rapid as in the current study, or can slow but persistent weight loss also ultimately result in a similar improvement in vascular function? If caloric restriction alone was sufficient to improve endothelial function, one should be able to see an early effect in patients undergoing bariatric surgery. If, however, there is persistence in the generation of various mediators responsible for the endothelial dysfunction, these factors may make it difficult to detect any significant improvements in endothelial function for long periods. This is consistent with persistent elevations in the levels of markers of endothelial activation and inflammation for several months after bariatric surgery.\(^10\) Nevertheless, it is reasonable to postulate that patients with lesser degrees of overweight/obesity, without other comorbidities, will experience a significant improvement in endothelial function over time, as long as they achieve significant weight loss, even if the rate of weight loss is not exceptionally rapid.

Although not enough is known about the effect of macronutrients on vascular function, it appears clear that the macronutrient composition of a diet may affect endothelial function independent of the effect of the weight loss itself.
The diet in the current study was low in fat with slightly reduced amounts of carbohydrate and protein. Interestingly, in a different study\(^7\) comparing the effects of a low-carbohydrate versus a low-fat diet, despite similar degrees of weight loss, the low-fat diet group showed a significant improvement in endothelial function, whereas the low-carbohydrate diet group showed no change in endothelial dysfunction. Furthermore, it is highly likely that sodium intake is also reduced in proportion with the caloric restriction, although no information regarding sodium intake is provided in the current study. From a vascular function perspective, a reduction in sodium intake is likely to affect endothelial function, either directly or indirectly, and this factor should be considered when evaluating the effects of dietary interventions on vascular function.

What are the mechanism(s) responsible for the improvement in vascular function resulting from weight loss? There is scant information available regarding any such possible mechanisms. Indeed, it is the lack of significant association between changes in various measured variables and the change in endothelial function, rather than the few positive associations seen in the current study, that is perhaps more reflective of the current level of understanding of the role of various mediators in obesity-related vascular dysfunction. For instance, adiponectin has been proposed to exhibit vascular protective properties. Although this may be true under certain experimental conditions, the results of this study caution against a positive conclusion regarding adiponectin. The results of the current study showing no relation between adiponectin and the improvement in endothelial function are in line with our own experience at Indiana University; our data suggested that, not only was adiponectin not directly associated with endothelial function, but instead might actually be involved in fuel partitioning.

Finally, if excessive adiposity leads to endothelial dysfunction, does any 1 fat depot play a more significant role than the others? Is visceral fat more detrimental than subcutaneous fat? The answer is not simple, because the former depends on the inability of the latter to enlarge. In other words, visceral adipose tissue mass may be a marker of the inability to store more fat in subcutaneous tissue rather than a risk factor in its own right. It is possible that once subcutaneous fat storage reaches a threshold, inflammatory signals are generated and macrophages recruited to initiate a cascade of signals that simultaneously lead to insulin resistance and endothelial dysfunction, whereas additional fat is stored offsite in susceptible tissues, such as skeletal muscle, liver, pancreas, and visceral fat depots. In keeping with this concept is the observation\(^11\) that, in the early phase of weight loss, there is similar or greater reduction of peripheral subcutaneous adipose tissue as compared with visceral adipose tissue. Thus, once the peripheral tissue is again available for fat storage, other tissues can unload their excessive fat depots with a parallel decrease in inflammatory mediators and improvement in insulin sensitivity and endothelial function (Figure).

In conclusion, the current study adds to the body of evidence supporting a relationship between weight loss and improvement in endothelial function, which, in turn, implies reduced cardiovascular risk. However, there is clearly an urgent need for additional robust studies in both the human and preclinical models to further our understanding of the mechanisms underlying the benefits of weight loss on vascular function.

Disclosures

None.

References

Weight Loss and Vascular Function. The Good and the Unknown
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