OBESITY IS A RISK FACTOR for atherosclerotic heart disease and a major cause of morbidity and mortality throughout the world. In the United States, the incidence of obesity and insulin resistance has risen dramatically in the past decade, with an adult prevalence of 32% (19). Nonsurgical treatment strategies for obesity include diet, exercise, and behavioral therapy. Public awareness of the “obesity epidemic” resulted in the popularization of dietary weight loss strategies such that 45% of American women and 30% of American men now diet to lose weight (26). The Atkins diet, modeled on low-carbohydrate intake, has received considerable public attention as a desirable mode of dietary weight loss (1). The nutrient-specific effects of this diet on cardiovascular health are largely unknown and controversial due to the replacement of carbohydrate with fat calories (1). This has important implications in the context of the dyslipidemia that occurs during metabolic syndrome.

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Focardi et al. (6) have identified a novel restorative effect of low-carbohydrate diet on coronary endothelial function in the Zucker rat model of metabolic syndrome. In this study, obese (OZR) and lean (LZR) Zucker rats were fed low- (LC; 10% carbohydrate) or normal (NC; 59% carbohydrate)-carbohydrate diet for 3 wk ad libitum (6). Endothelial function was tested in vitro with application of acetylcholine (ACh) and intraluminal flow [flow-induced dilation (FID)] in isolated coronary arterioles. Whereas OZR had higher body weights versus LZR, there was no change in body weight during the course of the study because LC and NC diets had similar caloric intakes. Similar to previous studies (21), endothelium-dependent vasodilation was impaired during metabolic syndrome. The novel finding of the current study was that OZR on a LC diet demonstrate improved FID and ACh responses when compared with NC diet. Interestingly, nitric oxide (NO) synthase (NOS) inhibition with Nω-nitro-L-arginine methyl ester (L-NAME) had no effect on this restored dilation (6). In contrast, ACh dilation and FID in coronary arterioles of LZR on NC and LC were reduced with L-NAME, suggesting that the LC effects on endothelium are different in metabolic syndrome. The authors conclude that improved endothelium-dependent dilation in OZR on LC diet involves a NO-independent mechanism. This finding suggests a novel alternative compensatory mechanism in OZR on LC diet.

The lack of weight loss and the maintained caloric intake in LZR and OZR during LC diet may limit the clinical relevance of this study since patients taking an isocaloric LC diet eat less food and lose more weight (at least initially) compared with those on conventional low-fat diets (7). However, major strengths are derived from the ability to ask whether the benefits of dietary interventions on vascular health occur without significant weight loss. The Zucker obese rat model may be nicely suited to answer questions regarding the nutrient-specific effects of dietary interventions on vascular health since ad libitum feeding likely results in weight gain due to leptin receptor deficiency. Calorie restriction was not studied, but the findings of this report indicate that improved endothelial function during LC diet is macro-nutrient specific and independent of weight loss. Future analysis of the weight loss effects on endothelium in OZR may require calorie restriction.

An interesting finding of the present study is that FID and ACh responses in OZR were not restored to levels similar to those in LZR. Although direct vascular measurements of NO were not made, it is possible that this difference between LZR and OZR is related to persistence, albeit at a lower level, of ROS-induced reduction of NO-mediated dilation. Carbohydrate calories are replaced with fat calories on a LC diet. Since even a single high-fat meal reduces NO bioavailability (23), it is possible that high fat on LC diet reduces NO in OZR. However, vasodilation and blood lipids in LZR were unaffected by LC diet, arguing against high dietary fat during LC diet as a mechanism for reduced NO in OZR.

Characterization of the dietary influence on endothelial function will necessitate further study. For example, diet durations longer than 3 wk provide greater restoration of NO, but this is unlikely without improvements in fat mass, cholesterol, or insulin resistance (2), which were not observed in the present study (6). It will be important to establish whether longer durations of LC dieting restore NO in this model. On the other hand, antioxidant supplementation of the LC diet may yield a restoration of NO bioavailability in OZR, thereby improving endothelial function to LZR levels. Uncoupling of NOS occurs during diabetes (27), making supplementation with tetrahydrobiopterin to restore NOS coupling another important area for exploration (13). Accordingly, evaluation of the nutrient-specific effects of LC diets on NOS function represents an exciting area for future investigation.

The effects of metabolic syndrome on endothelial function are well characterized and involve an oxidant mechanism (22). Although the exact source of reactive oxygen species (ROS) generation is unclear in this model, most cardiovascular risk factors are associated with elevations in ROS that reduce NO (20, 24). Endothelial dysfunction induced by acute hyperglycemia or hypercholesterolemia, two major components of the metabolic syndrome, are reversed by antioxidant treatment (3, 28) and may be improved on LC diet. However, triglycerides and cholesterol were not elevated during LC diet in this study and are not associated with endothelial function during hypoca-
loric diet in the current study was concurrent with continued dyslipidemia and insulin resistance in OZR (6). In addition, there was no change in blood lipids in LZR on LC diet, arguing against blood cholesterol changes with high dietary fat as a mechanism for reduced NO. Since Focardi et al. (6) reported virtually no change in cholesterol or insulin resistance during LC, this study supports a novel mechanism of diet-induced improvement in endothelial function, independent of insulin resistance, weight loss, and other cardiovascular risk factors.

Alternative to improved vascular sources of ROS, obesity is associated with a chronic inflammation involving serum adipokines and cytokines produced by fat that adversely affect endothelial cell function either directly or through oxidative mechanisms (15, 31). Circulating cytokines and other indices of ROS were not determined. However, other studies suggest that OZR manifest elevations in these markers of inflammation, warranting future studies evaluating the oxidative changes on LC diet. Loss of fat mass may reduce inflammation and increase NO (31). Therefore, supplementation of LC diet with antioxidants known to protect against the negative effects of hyperlipidemia and hyperglycemia on endothelial function and/or interventions that reduce fat mass (e.g., exercise) may fully restore NO function during metabolic syndrome.

The maintained vasodilation in OZR on LC diet represents a novel compensation mechanism for reduced NO-dependent endothelial function during metabolic syndrome. Compensation for reduced NO bioavailability by endothelium-derived hyperpolarizing factors (EDHF) has been described in other vascular beds (10) and the human heart (18). The exact nature of EDHF is still under investigation but may include the metabolic products of cytochrome (CYP) P-450 epoxyeicosatrienoic acids (EETs) (14). Alternatively, hydrogen peroxide (H2O2) acts as an EDHF in the mesenteric and coronary microcirculation (16, 17). Unlike NO, vasodilation to EDHF is maintained during cardiovascular disease when ROS are elevated. While the authors did not determine whether the EDHF is maintained during cardiovascular disease when ROS were not determined. However, other studies suggest that OZR manifest elevations in these markers of inflammation, warranting future studies evaluating the oxidative changes on LC diet. Loss of fat mass may reduce inflammation and increase NO (31). Therefore, supplementation of LC diet with antioxidants known to protect against the negative effects of hyperlipidemia and hyperglycemia on endothelial function and/or interventions that reduce fat mass (e.g., exercise) may fully restore NO function during metabolic syndrome.

Taken together, these data implicate EDHF in the restored vasodilation during 3-wk LC diet in metabolic syndrome. The exact nature of the maintained dilation is unknown in OZR but may involve EETs or H2O2, as reported in multiple vascular beds during disease (9, 11, 18). The study of EDHF in models of insulin resistance is important, given the stimulatory effects of EETs on fatty acid β-oxidation (5) and their beneficial effects on insulin sensitivity (30). Since EDHF-mediated dilation is reduced during insulin resistance (11) and CYP P-450 expression is decreased in OZR (29), LC diets may provide important protective effects on vascular endothelial health during metabolic syndrome.

In conclusion, the report by Focardi et al. (6) demonstrates a novel mechanism of improved coronary vascular function with LC diet during metabolic syndrome. This study implicates a role for EDHF in dietary interventions that may improve the cardiovascular complications of metabolic syndrome. Thus future studies are needed to determine the macronutrient effects of diet on vascular health during and health.

REFERENCES


