A Look at the Low-Carbohydrate Diet
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Most fad diets are just that — a bright flash that quickly fades, only to be followed by another best-seller and a new face on the talk-show circuit. The high-fat, high-protein, low-carbohydrate (HPLC) diet has outlived the rest of the pack. This diet clearly has its supporters. In many ways, it is attractive to believe that manipulation of macronutrient composition might control body weight and improve health. However, a recent study by Foo and colleagues\(^1\) shows that HPLC diets may accelerate atherosclerosis through mechanisms that are unrelated to the classic cardiovascular risk factors.

Given the associations between a high intake of saturated fat and cardiovascular diseases, many scientists have sounded the alarm that HPLC diets might increase the risk of heart-related disorders. However, the HPLC diet has been associated with short-term improvement in many of the classic intermediate cardiovascular risk factors, such as levels of low-density lipoprotein and high-density lipoprotein cholesterol and blood pressure.\(^2,3\)

Foo et al. tested the effect of different diets on mice that were deficient in apolipoprotein E. These mice are especially susceptible to atherosclerosis when fed a so-called Western high-fat, moderate-protein, and moderate-carbohydrate diet. They put one group of mice on a diet of standard laboratory chow, another group on a Western diet, and a third group on an HPLC diet. Instead of measuring plasma risk factors, the investigators directly measured the formation of arterial plaque — and found two times more plaque in the arteries of animals that were fed the HPLC diet than in those that were fed the “atherosclerotic” Western diet (Fig. 1).

A common misconception is that HPLC diets lead to greater weight loss than traditional diets. In general, they do not,\(^3\) but nonetheless, mice that were fed the HPLC diet gained less weight than the mice on a Western diet. Cholesterol levels were elevated in the mice that were fed the HPLC diet and those fed the Western diet, as compared with mice that were fed standard chow, but there was no significant difference in the cholesterol levels of mice on the Western diet and those on the HPLC diet.

So why did the mice on the HPLC diet have more atherosclerosis? Here is where it gets really interesting. Experiments that were subsequently carried out by Foo et al. suggest a couple of reasons.

First, levels of nonesterified fatty acids (NEFAs) in the mice on the HPLC diet were nearly twice those in mice that were fed the other two diets. There is strong epidemiologic evidence showing an association between NEFAs and atherosclerotic events and a growing consensus that a high level of NEFAs is a risk factor for cardiovascular disease.\(^4\) Free fatty acids (including NEFAs) are released from insulin-resistant adipocytes in obesity, and several studies have shown that NEFAs cause activation of inflammatory pathways in multiple tissues.

Second, mice on the HPLC diet, but not the Western diet, showed markedly low numbers of circulating endothelial progenitor cells (EPCs). These cells, which were first identified almost a decade ago, are formed in the bone marrow and released into the bloodstream. As circulating mononuclear cells, they participate in the repair of damaged vessel walls and improve endothelial function through undefined mechanisms. Several investigators have observed a reduction in the number of EPCs in patients with atherosclerosis,\(^5\) a finding that was strikingly similar to that of Foo et al. The number of EPCs is also decreased in patients with type 2 diabetes, a disease that is associated with an increased risk of atherosclerosis. Since the publication of these early clinical reports, the link between a reduced number of circulating marrow-derived EPCs, vascular dysfunction, and atherosclerosis has been well...
supported through additional research, although the mechanisms that link EPCs to a healthy vasculature and a blunting of the atherosclerotic process are not yet understood.

Traditionally, the atherosclerotic risk profile that is associated with specific diets is determined by measuring intermediate risk factors, such as levels of low-density lipoprotein cholesterol.

Figure 1. High-Protein, Low-Carbohydrate (HPLC) Diet and Atherosclerosis.
A recent study by Foo et al. suggests that an HPLC diet promotes atherosclerosis through mechanisms that do not modify the classic cardiovascular risk factors. They studied mice that were fed standard laboratory chow (Panel A), a so-called Western diet (Panel B), or an HPLC diet (Panel C). They found that mice that were fed the HPLC diet had almost twice the level of arterial plaque as mice that were fed a Western diet. The classic risk factors did not differentiate these two groups of mice, even though both were fed atherogenic diets. Normally, endothelial progenitor cells are released from the bone marrow and home in on damaged endothelium to promote repair and maintain normal vascular reactivity. The mice that were fed the HPLC diet had markedly fewer circulating endothelial progenitor cells and higher levels of nonesterified fatty acids than mice that were fed the Western diet. LDL denotes low-density lipoprotein.
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terol, blood pressure, and C-reactive protein. The work of Foo et al. suggests that the HPLC diet might increase the risk of cardiovascular disease through mechanisms that have nothing to do with these “usual suspects” and so provides a note of caution against reliance on the traditional cardiovascular risk factors as a gauge of safety.

Fortunately, both EPCs and NEFAs are easily measured in the research clinic. A focused study should be conducted to examine whether the HPLC diet produces the same effects on EPCs and NEFAs in humans as it does in mice. In the meantime, the ageless advice applies to the consumer of the HPLC diet and other fad diets: caveat emptor.

Dr. Smith reports receiving consulting fees from Unilever. No other potential conflict of interest relevant to this article was reported.

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