Optimizing the cardiovascular outcomes of weight loss\textsuperscript{1,2}

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The past 2 y have seen a steady stream of reports indicating that restriction or modification of carbohydrate intakes can favorably affect weight loss and cardiovascular disease (CVD) risk factors (1–6). The article by Ebbeling et al (7) in this issue of the Journal represents one more in favor of diets with a low glycemic index (GI) or glycemic load (GL). Serum triacylglycerol concentrations in young overweight adults with similar weight loss fell nearly twice as far with the ad libitum low-GI diet as with the energy-restricted low-fat diet, whereas concentrations of plasminogen activator inhibitor 1, an important measure of thrombogenicity, significantly worsened (ie, rose) in subjects who were following the energy-restricted low-fat diet. The study was small (n = 23) and from a group at Harvard that had published other studies on the same topic, but it was long-term (12 mo) and carefully carried out.

That lowering daylong glycemia, with or without weight loss, might improve CVD risk should not come as a surprise. Many intervention studies have tested the hypothesis that low-GI diets will improve not only glucose control but also lipid metabolism. Twenty years ago, Jenkins et al (8) showed in 3-way crossover studies that low-GI diets improve triacylglycerol and total cholesterol concentrations in hyperlipidemic subjects more than do conventional low-fat diets. Recently, Patel et al (9) showed that women with advanced CVD who were awaiting bypass surgery spent significantly fewer days in the hospital than did their counterparts who were following a conventional low-fat diet (7.1 and 9.5 d, respectively). Slowing the rate of carbohydrate absorption per se by using the α-glucosidase inhibitor acarbose was found to reduce cardiovascular events by \(\approx 50\%\) over 3 y in a large population with impaired glucose tolerance (IGT).

Long-term studies in animals have provided additional evidence that the GI itself, and not fiber intake or any other confounding factor, is important in relation to weight gain, body fat, and CVD risk. Animals fed diets differing only in the type of starch (high- or low-GI) gained body fat faster with the high-GI diet than with the low-GI diet (10). Even when fed to similar body weight, high-GI diet–fed rats have more body fat (71\%), less lean body mass, and higher plasma triacylglycerol concentrations than low-GI diet–fed rats (11).

Large-scale observational studies show links—even in non-diabetic persons—between the presence of postchallenge hyperglycemia and an increased risk of chronic disease (12). In a meta-analysis of 39 prospective studies of non-diabetic cohorts, Levitan et al (13) found that groups with the highest 120-min postload glucose concentration had a 27\% greater risk of CVD than did those with the lowest glucose concentrations, and the relative risk was higher in women than in men (1.56 and 1.23, respectively). Adjustment for traditional CVD risk factors attenuated but did not abolish the relation. Moreover, Liu et al (14) showed that average dietary GI and GL were also independent predictors of 10-y prospective CVD risk in US women. The latter study is particularly important, because it implies that postprandial glycemia induced by carbohydrate foods in everyday settings (and not glucose tolerance testing) is clinically relevant.

There has been fundamental progress in showing that glucose itself can directly damage vascular cells, by a variety of mechanisms. All of these mechanisms appear to reflect a single hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain (15). Normal concentrations of glycemia such as those encountered during a standard meal have been shown to acutely decrease plasma antioxidant capacity, which reflects a significant oxidative stress. Moreover, the vascular endothelium is a prime target because endothelial cells, unlike many other cells in the body, are unable to regulate glucose transport across the cell membrane.

Taken together, intervention, observational, and experimental studies suggest that postprandial glycemia plays a greater role in CVD than is generally acknowledged, perhaps more so in women than in men. Because decreasing the intakes of total and saturated fat has been the goal of efforts to reduce the incidence of obesity and CVD, high-carbohydrate foods have been recommended, not so much because of their intrinsic nutritional merit, but because they fill the calorie space formerly occupied by fat. But one of the more subtle changes in the food supply over the past few decades has been the replacement of traditionally processed grains by more highly processed, high-GI cereal products. Less-processed foods are more likely to contain slowly digested carbohydrates because the starches and sugars remain closely embedded in the plant’s original botanical structure, surrounded by bran and other barriers that inhibit starch gelatinization. In contrast, modern methods of food production using finer flours, extrusion technology, and high temperatures and pressures increase starch gelatinization and thus the rate of digestion in vivo. Compared with sugars, high-GI starch foods receive little attention, and yet they have a greater capacity than do sugars to...

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increase the glycemic and insulinotrophic potency of the whole diet.

Because the overweight are now the majority in most industrialized nations, we can no longer afford to direct dietary guidelines to just the “healthy” population. Moreover, we need efficacious guidelines that work in practice, not just in theory. During the past 2 decades, when low-fat diets and plenty of cereal foods were actively promoted, health trends were the opposite of those we would wish. Along with obesity, the diagnoses of type 2 diabetes and IGT have soared, “maturity-onset” diabetes is being diagnosed in children, and the metabolic or insulin resistance syndrome affects 1 in 4 adults. Even normal-weight individuals can have the metabolic syndrome and thus a higher risk of CVD. Diseases such as polycystic ovarian syndrome, nonalcoholic steatohepatitis, and fatty liver, which have their roots in insulin resistance, have also reached alarming proportions.

It must now be clear that the conventional low-fat diet (with no consideration of the nature of the starch) is not the ideal diet for most of the population. Dietary Guidelines for Americans 2005 (16) sensibly gives greater emphasis to increased consumption of whole grains rather than to refined grains. However, this is unlikely to improve daylong glycemia, because many so-called whole-grain breads and breakfast cereals produce as much postprandial glycemia as do their white-flour counterparts (17). Moreover, recommending whole-grain and high-fiber cereals is nothing new—nutritionists have been doing that for at least 50 y. A high proportion of the population will dismiss outright any suggestion of eating whole grains or whole meal. We urgently need nutrition messages that fire the imagination and encourage even unmotivated people to adopt effective dietary strategies that reduce the risk of chronic disease. In Australia and the United Kingdom, the GI has become a popular concept in its own right. The message that slowly digested carbohydrates can “keep you fuller for longer” is one that the general public, young and old, intuitively understands. Indeed, many people warm to a plan that “fills you fuller for longer” is one that the general public, young and old, intuitively understands. Indeed, many people warm to a plan that...

REFERENCES