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Low-fat diets, lipoprotein subclasses, and heart disease risk[1,2]

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Current dietary guidelines emphasize reductions in dietary fat, particularly saturated fat, for the hygienic control of plasma lipoproteins. This recommendation is based on abundant scientific evidence showing that low-fat diets reduce plasma cholesterol, particularly LDL. The low rate of heart disease in cultures that traditionally eat low-fat diets is manifest. However, low-fat diets also reduce plasma concentrations of HDL cholesterol (1). This leads to the obvious question of whether reductions in both atherogenic LDL cholesterol and antiatherogenic HDL cholesterol translate into reduced heart disease risk in normolipidemic men and women.

In this issue, Berglund et al (2) examine the effects of feeding low-fat diets on HDL subclasses in a multiracial, multigenerational sample of normolipidemic men and women. Their study, carefully designed and successfully implemented, assessed the effect of the diets on HDL_2- and HDL_3-cholesterol concentrations and on their percentage distribution within 5 HDL subclasses. Switching from an average American diet to the American Heart Association Step I diet reduced both HDL_2- and HDL_3-cholesterol concentrations. The HDL-subclass distribution shifted toward smaller particles, with reductions in the percentage area for HDL_{2b} and increases in the percentage area for HDL_{3a}, HDL_{3b}, and HDL_{3c}. These changes in the distribution of HDL subclasses suggest a less antiatherogenic HDL profile with consumption of a low-fat diet.

These results from the Dietary Effects on Lipoproteins and Thrombogenic Activities (DELTA) Study are consistent with those of an earlier study involving 105 men (3). When the men switched from a 6-wk high-fat to a low-fat diet in a crossover study, HDL_{2a}, HDL_{2b}, and HDL_{3a} concentrations decreased significantly. In contrast with measurements of HDL subclasses in the DELTA Study, this earlier study did not measure the relative area of the HDL subclasses, but rather the absolute area (assumed to be proportional to plasma concentrations). Expression of the areas as percentages necessarily causes an inverse correlation between the larger and smaller subclasses, which may have obscured reductions within the HDL_{2a} and HDL_{3a} regions in the DELTA Study. As recognized by the authors, the apparent inconsistency between HDL_3 responses (which decreased with the low-fat diet) and HDL_{3a}, HDL_{3b}, and HDL_{3c} responses (which increased with the low-fat diet) may have been due to technical differences in the subclass measurements. In cross-sectional samples, variations in plasma HDL_3-cholesterol concentrations tend to be correlated with electrophoretic measurements of HDL_{2a}, HDL_{2b}, and HDL_{3a}, but not with HDL_{3b} (4).

Although Berglund et al suggest that reductions in LDL particle number may offset any potential negative effect of a reduction in overall HDL, HDL_2-cholesterol, or HDL_{2b} concentrations, this benefit may not apply to all individuals. Although the DELTA Study investigators showed that HDL and other lipoprotein responses to low-fat diets did not differ significantly by sex, age, or race, in this and other studies, considerable interindividual variation in responses was observed (1, 3, 5, 6). Among the traits known to increase the magnitude of the LDL-cholesterol response to low-fat diets are genotype, such as the presence of the apo E4 isoform, and other factors leading to higher baseline LDL-cholesterol concentrations (6, 7). Another phenotype that can affect the response of both LDL and HDL to low-fat diets is variation in LDL particle size profiles (3, 5). A predominance of small, dense LDL particles (LDL subclass pattern B) is associated with higher triacylglycerol concentrations and a 3-fold increased risk of coronary artery disease when compared with the alternative, pattern A (8). Men expressing the LDL pattern B with consumption of a high-fat diet show significant diet-induced decreases in both LDL cholesterol and apolipoprotein (apo) B, suggesting a decrease in the number of LDL particles and possibly a relatively more favorable effect on coronary heart disease (CHD) risk (5). In contrast, those expressing LDL pattern A do not show a decrease in apo B concentrations. The men with LDL pattern A also show smaller decreases in LDL cholesterol and greater decreases in HDL_{2b} than do men with LDL pattern B men when consuming low-fat diets, and nearly twice the estimated increase in CHD risk assessed by the Framingham score (**Figure 1**). Moreover, a subset of low-risk, pattern A men convert to pattern B when switched from a high-fat to a low-fat diet (3). Reduced LDL particle size in these men was associated with decreases in HDL_{2b} and increases in plasma triacylglycerol concentrations, suggesting that these lipoprotein responses may be linked metabolically (3). It is not known which of the various lipoprotein indexes used in these studies provides the best prediction of risk of developing coronary artery disease, but overall

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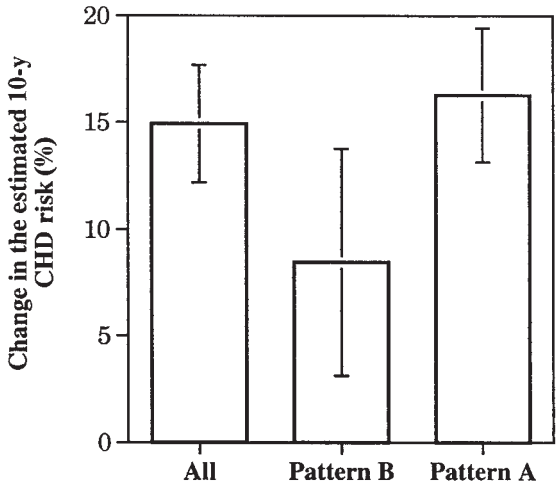

FIGURE 1. Mean (±SE) percentage changes in estimated 10-y coronary heart disease risk (10) when 105 healthy normolipidemic men (5) switched from a diet providing 45% of energy as fat to a diet providing 24% of energy as fat, by LDL-subclass pattern. The increase in projected risk was significant in the total sample and in men with LDL pattern A ($P < 0.001$).

the results suggest that high-risk individuals, such as those with elevated LDL-cholesterol concentrations or small, dense LDL particles, or both, may be the most appropriate candidates for diets low in total fat (eg, providing much less than 30% of energy), whereas the apparently adverse metabolic changes with such diets may be of particular concern to those individuals who have lipoprotein profiles indicating a low risk of CHD while consuming their usual diets.

Another important consideration in assessing the metabolic response to diets low in total and saturated fat is the influence of the nutrients that are substituted for fat. In particular, it has been shown that increased carbohydrate intakes lead to increases in plasma triacylglycerol and accompanying reductions in HDL cholesterol, LDL particle size, and insulin sensitivity. The type of carbohydrate may also be important. Thus, the influence of low-fat diets on CHD risk is dependent on both the overall nutrient composition of such diets and the interindividual differences in response to these nutrients.

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