Symposium: Nutritional and Metabolic Diversity: Understanding the Basis of Biologic Variance in the Obesity/Diabetes/Cardiovascular Disease Connection

Atherogenic Lipoprotein Phenotype and Diet-Gene Interactions$^{1,2}$

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ABSTRACT Studies employing analysis of LDL subclasses have demonstrated heterogeneity of the LDL response to low fat, high carbohydrate diets in healthy nonobese subjects. In individuals with a genetically influenced atherogenic lipoprotein phenotype, characterized by a predominance of small dense LDL (LDL subclass pattern B), lowering of plasma LDL cholesterol levels by diets with ≤24% fat has been found to represent a reduction in numbers of circulating mid-sized and small LDL particles, and hence an expected lowering of cardiovascular disease risk. In contrast, in the majority of healthy individuals with larger LDL (pattern A, found in ~70% of men and a larger percentage of women), a significant proportion of the low fat diet–induced reduction in plasma LDL cholesterol is made by depletion of the cholesterol content of LDL particles. This change in LDL composition is accompanied by a shift from larger to smaller LDL particle diameters. Moreover, with progressive reduction of dietary fat and isocaloric substitution of carbohydrate, an increasing number of subjects with pattern A convert to the pattern B phenotype. Studies in families have indicated that susceptibility to induction of pattern B by low fat diets is under genetic influence. Thus, diet-gene interactions affecting LDL subclass patterns may contribute to substantial interindividual variability in the effects of low fat diets on coronary heart disease risk. J. Nutr. 131: 340S–343S, 2001.

KEY WORDS: • cholesterol • LDL • diet • fat • carbohydrate • lipoprotein subclasses

Current dietary guidelines for the prevention and treatment of atherosclerotic cardiovascular disease include a strong emphasis on maintaining optimal LDL cholesterol levels, principally by limiting intake of saturated fat and cholesterol in the context of diets that are also limited in total fat (<30% of energy). On average, such diets do achieve significant reductions of total and LDL cholesterol; however, the magnitude of change varies substantially among individuals (Katan and Beynen 1987, Schaefer et al. 1997), with many showing either little change or even increases in these parameters. Moreover, low fat, high carbohydrate diets can also result in reduced plasma HDL cholesterol and/or increased triglyceride, raising the possibility that these changes may offset to varying degrees the expected benefit of LDL cholesterol lowering. The wide interindividual variations in lipoprotein response to altered dietary composition have been attributed at least in part to genetic differences among individuals (Dreon and Krauss 1997, Ordovas 1999, Schaefer et al., 1997). Although a number of studies have demonstrated associations of these variations with polymorphisms in candidate genes (Dreon and Krauss 1997, Ordovas 1999), the magnitude of these effects has generally been small, and it is likely that multiple factors, many as yet unrecognized, are involved.

Atherogenic lipoprotein phenotype

In recent years, identification of distinct LDL subclasses that differ in particle size and density has led to recognition that these subclasses differ in their metabolic and pathologic properties, as well as their dietary and genetic determinants (Krauss 1997). Moreover, there is variation in the distribution of these subclasses among individuals. In the majority of healthy subjects, the major forms of LDL are large and buoyant, but in a substantial subset of the population, there is a predominance of small, dense LDL particles (Austin et al. 1990). The small, dense LDL profile, designated LDL subclass pattern B, is associated with relative increases in plasma triglyceride and other proatherogenic metabolic changes, including increased intermediate density lipoproteins, reduced HDL...
cholesterol (Austin et al. 1990) and reduced insulin sensitivity (Reaven et al. 1993). Moreover, small LDL particles appear to have greater atherogenic potential than large LDL by virtue of reduced receptor-mediated clearance (Campos et al. 1996) and higher endothelial transport (Nielsen 1996), proteoglycan binding (Anber et al. 1997) and oxidative susceptibility (Tribble et al. 1992). Overall, this profile can result in approxi-
mately a threefold increase in risk for coronary artery disease (Austin et al. 1998, Gardner et al. 1996, Lamarche et al. 1997, Stamper et al. 1996), an observation that supports its designation as an atherogenic lipoprotein phenotype. The magni-
tude of the risk, however, is strongly dependent on overall plasma concentrations of apolipoprotein (apo)B-containing lipoproteins, suggesting that the quantity as well as the quality of LDL subfractions should be considered in assessing athero-
sclerosis risk.

**Genetic influences on LDL subclasses**

Studies in families have indicated that LDL subclass pat-
terns are influenced by major genes (Austin et al. 1988, Austin 1994); linkages of LDL particle size phenotypes to several candidate gene loci have been reported (Allayee et al. 2000, Austin et al. 1998, Nishina et al. 1992, Rotter et al. 1996, Talmud et al. 2000). To date, the most consistent evidence for linkage has been found for a locus in the vicinity of the LDL receptor gene on chromosome 19p (Nishina et al. 1992, Rotter et al. 1996), the apoCII gene locus on chromosome 11 (Al-
laye et al. 1998, Rotter et al. 1996) and the cholesteryl ester transfer protein gene on chromosome 16 (Rotter et al. 1996, Talmud et al. 2000). Thus, major genes may act singly or in combination to influence LDL particle size. Although a num-
ber of the linked genes have a plausible basis for contributing to variation in LDL subclass profiles, in the case of the LDL receptor gene, analyses of DNA sequences in the coding region (Naggett et al. 1997) as well as immediately upstream (Naggett, J.K., Nishina, P.M., Krauss, R.M., personal commu-
nication) showed no significant differences in pattern B vs.

**Gene-diet interactions involving small dense LDL**

Despite the evidence for major gene effects on LDL subclass patterns, studies in twins have indicated that heritability of LDL peak particle size as a quantitative trait is < 50% (Austin et al. 1993, Lamon-Fava et al. 1991). This is consistent with the strong influence of modifying factors on the expression of LDL subclass pattern B. Age and gender are major determin-
ants, with a prevalence of ~30% in men, 15–20% in post-
menopausal women and 5–10% in younger individuals (Aus-
tin et al. 1990 and 1993, Campos et al. 1992). In addition, LDL size is influenced by metabolic factors affecting plasma triglyceride (Krauss et al. 1988, McNamara et al. 1987), in-
cluding abdominal adiposity (Terry et al. 1989) and insulin resistance (Reaven et al. 1993).

Given the evidence for differences in the metabolic and pat-

tologic behavior among LDL subclasses and for both ge-

**FIGURE 1** Distribution of changes in LDL cholesterol between

![Distribution of changes in LDL cholesterol between high fat (46% energy) and low fat (24% energy) diets in 105 healthy men; [data from Dreon et al. (1994)].

men; [data from Dreon et al. (1994)].
A and B subjects (Dreon et al. 1994). Taken together, these results indicate that in the majority of men, the reduction in LDL cholesterol seen during consumption of a low fat, high carbohydrate diet is due in large measure to a shift from larger, more cholesterol-enriched LDL to smaller, cholesterol-depleted LDL, whereas much greater reductions in LDL cholesterol and a reduction in the number of smaller LDL particles are achieved in individuals with a predominance of small, dense LDL consuming a high fat diet.

These results, which have been confirmed in a second study in 133 men (Dreon and Krauss 1995), indicate that reduction in dietary fat and increase in carbohydrate can elicit the expression of LDL subclass pattern B in a subset of healthy men. Moreover, a short-term (10 d) dietary challenge of a 10% fat diet in 38 healthy men with pattern A consuming diets containing 20–24% fat resulted in a conversion to pattern B in 12 men (32%) (Dreon et al. 1999). There were no significant reductions in LDL cholesterol levels in the group as a whole, but those who converted to pattern B had significantly greater increases in levels of triglyceride and apoB and reductions in HDL cholesterol than those who remained pattern A (Dreon et al. 1999).

Overall, in a series of such studies employing diets with varying fat content and reciprocal variation in carbohydrate content, there is a strong linear relationship of decreased fat/increased carbohydrate intake with prevalence of LDL subclass pattern B in healthy men (Fig. 2). These results indicate that the prevalence of pattern B in men consuming 30% fat is ~30–35%, a figure that is consistent with the prevalence of pattern B in men in the general population (Austin et al. 1990, Campos et al. 1992). Hence, the results suggest that the short-term effects of variation in diet composition on LDL subclass phenotypes are indicative of the effects of long-term diet consumption.

Genetic influences on response of LDL subclass patterns to low fat diet

The results in Figure 2 indicate that dietary fat and/or carbohydrate intake are strong determinants of subclass pattern B, and may act to induce expression of this trait in susceptible individuals. Moreover, given the evidence for genetic effects on LDL subclass patterns, the results raise the possibility that induction of pattern B by a low fat, high carbohydrate diet is also under genetic influence. Heritability of this diet response has been demonstrated in two family studies involving premenopausal women (Dreon et al. 1997) and children (Dreon et al. 2000), groups with low expression of pattern B in whom genetic susceptibility to this trait was inferred by its presence in one or both parents. In both studies, prevalence of pattern B after consumption of a low fat diet was greatest in offspring of two pattern B parents.

On the basis of the evidence for heritability of induction of pattern B by a low fat diet, we hypothesized that one or more of the genes linked to variation in LDL particle size may be responsible for this diet effect. To test this hypothesis, we recently studied the effects of reduction in dietary fat from 40 to 20% of energy in a cohort of 298 brothers from 135 families in whom linkage to a polymorphism in the LDL receptor was tested by nonparametric sibpair linkage analysis (Krauss et al. 1999). Significant linkage was observed during consumption of both high and low fat diets, confirming earlier results in families in whom diet was not controlled. No genetic linkage was found for other lipid or lipoprotein variables, except for HDL cholesterol, which showed weak linkage to the LDL receptor gene (P < 0.05) for both diets. Interestingly, linkage of LDL subclass pattern (qualitative phenotype) was strong with consumption of the high fat diet, whereas linkages of quantitative measures (LDL density and size) were stronger with consumption of the low fat diet. Most notably, the tendency for a low fat diet to induce expression of LDL subclass pattern B was also linked to the LDL receptor gene. Therefore appears that the genetic locus on chromosome 19 that influences LDL subclass pattern with consumption of high fat diet also contributes to susceptibility for reduced size and increased density of LDL particles, and induction of the pattern B phenotype during consumption of a low fat diet. Thus, it is likely that one or more genes at this locus underlie diet-gene interactions affecting LDL subclass phenotypes.

SUMMARY

There is increasing awareness of the potential for genetic variation among individuals to influence nutrient requirements and biological responses to nutrient intake (Simopoulos 1999). In the case of genes influencing LDL subclass patterns, gene-diet interactions contribute to wide interindividual differences in the effects of low fat, high carbohydrate diets on risk for coronary heart disease. The recognition of such differences in metabolic response is prompting greater attention to the potential for individualization of nutritional approaches for prevention of heart disease (Krauss et al. 1996). Once specific genes responsible for these effects are identified, it will be possible to use this information to target low fat dietary interventions more effectively to those individuals most likely to achieve a benefit for cardiovascular disease risk (Krauss 2000).

LITERATURE CITED


