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REVIEW

Atherogenic Dyslipidemia: Cardiovascular Risk and Dietary Intervention

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Abstract Atherogenic dyslipidemia comprises a triad of increased blood concentrations of small, dense low-density lipoprotein (LDL) particles, decreased high-density lipoprotein (HDL) particles, and increased triglycerides. A typical feature of obesity, the metabolic syndrome, insulin resistance, and type 2 diabetes mellitus, atherogenic dyslipidemia has emerged as an important risk factor for myocardial infarction and cardiovascular disease. A number of genes have now been linked to this pattern of lipoprotein changes. Low-carbohydrate diets appear to have beneficial lipoprotein effects in individuals with atherogenic dyslipidemia, compared to high-carbohydrate diets, whereas the content of total fat or saturated fat in the diet appears to have little effect. Achieving a better understanding of the genetic and dietary influences underlying atherogenic dyslipidemia may provide clues to improved interventions to reduce the risk of cardiovascular disease in high-risk individuals.

Keywords Lipids · Lipoproteins · Cardiovascular diseases · Genetics

Definition of Atherogenic Dyslipidemia

Prospective epidemiologic studies have shown that blood levels of low-density lipoprotein cholesterol (LDL-C) significantly predict incident atherosclerotic cardiovascular disease (CVD), and LDL-C-lowering therapy has been repeatedly demonstrated in many populations to reduce CVD risk. This has led to the formulation of risk prediction algorithms for identification of high-risk individuals and specific LDL-C goals to be achieved with lifestyle and pharmacological interventions [1]. Many individuals with normal LDL-C levels nevertheless develop CVD [2], particularly in older age groups.

There is considerable heterogeneity among low-density lipoproteins (LDL), ranging from small, dense, lipid-depleted particles to large, buoyant cholesterol-enriched particles [3]. These particles have typically been grouped into four categories ranging from LDL1 (largest) to LDL4 (smallest) and subdivided even further into as many as eight subfractions. A number of studies have suggested that small LDL particles carry disproportionate atherogenic risk [4–7]. This suggests that treatment based on LDL-C levels alone potentially provides a suboptimal treatment for a significant proportion of at-risk individuals.

High-density lipoprotein cholesterol (HDL) also has a strong epidemiological relationship with CVD, with increased HDL-C levels protective against disease, and is divided into two to three subfractions. As with LDL-C, some studies suggest that specific HDL subfractions are more predictive of CVD than HDL-C [8], whereas others suggest no distinction [9–13].

Austin et al. first described a risk-conferring lipid/lipoprotein profile, termed "atherogenic dyslipidemia" or the "atherogenic lipoprotein phenotype," that comprises a higher proportion of small LDL particles, reduced HDL-C, and increased triglycerides [14]. Atherogenic dyslipidemia is characteristically seen in patients with obesity, the metabolic syndrome, insulin resistance, and type 2 diabetes mellitus [15, 16] and has emerged as an important marker for the increased CVD risk observed in these populations. Herein we review the present understanding of the

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contribution of atherogenic dyslipidemia to CVD, as well as the genetic and dietary influences underlying atherogenic dyslipidemia.

Small LDL Particles, Total LDL Particles, and CVD Risk

Besides the traditional blood lipid measurements of LDL-C, HDL-C, and triglycerides, there now exist a number of alternative measures that assess lipoprotein subfractions in some way. The best established is the measurement of the blood concentration of apolipoprotein B (apoB). Each non-HDL particle—including LDL particles, intermediate-density lipoprotein (IDL) particles, very-low-density lipoprotein (VLDL) particles, chylomicrons, and their remnants—typically harbors one apoB molecule. Thus, the apoB measure represents a count of non-HDL particles circulating in the bloodstream. More sophisticated techniques can quantify the numbers of particle within each lipoprotein class, as well as within subfractions of each lipoprotein class; in addition, peak particle size within a class (e.g., LDL peak particle diameter) can be calculated. These techniques include analytical ultracentrifugation, gradient gel electrophoresis, nuclear magnetic resonance (NMR), and a relatively new gas-phase differential electrophoretic macromolecular mobility-based method (termed as the ion mobility method).

A number of studies have now used one of the lipoprotein subfraction measurement techniques to assess whether any of the subfractions have prognostic power for CVD or intermediate endpoints for CVD such as coronary calcium score or carotid intima-media thickness. Notably, many of these studies find that the small LDL particle concentration predicts cardiovascular endpoints comparably to if not better than LDL-C [7, 17–21].

There is biological plausibility for a causal role of small LDL particles in atherosclerotic disease, with evidence that small, dense, lipid-poor LDL particles may be inherently more atherogenic than large LDL particles [6]. They have greater susceptibility to oxidation than larger particles and thus may be more likely to instigate the inflammatory processes in vascular endothelium that underlie atherosclerotic disease. They bind more tightly to arterial proteoglycans and may penetrate into the arterial wall more easily. Finally, small LDL particles have relatively lower affinity for the LDL receptor compared to mid-size particles, resulting in decreased cellular uptake and increased time spent circulating in the bloodstream, where the particles would have prolonged influence on the atherosclerotic process.

However, each of the studies that have demonstrated that small LDL particle concentrations are predictive of cardiovascular endpoints also showed that the total LDL particle number (LDL-P) is similarly predictive [7, 17–21]. This is because the small LDL particle number is highly correlated with LDL-P. Intuitively, this can be explained by the reasoning that among individuals with equal LDL-C levels, the same of amount of cholesterol distributed among a larger number of particles implies that the particles must be of smaller size on average. It is possible, then, that all LDL particles are similarly atherogenic and the association of increased small LDL particle concentrations with disease is simply the result of the increased number of LDL particles, rather than small LDL particles being uniquely atherogenic. Epidemiological studies to date have not been able to unequivocally distinguish between these two possibilities.

Regardless of whether the small LDL particle number or LDL-P is used, either offers prognostic information distinct from the standard LDL-C measure obtained with a fasting lipid profile. Reinforcing this point was the finding in the Framingham Offspring Study that when participants were divided into four groups—low LDL-C + low LDL-P, low LDL-C + high LDL-P, high LDL-C + low LDL-P, high LDL-C + high LDL-P—stratification by LDL-P markedly discriminated by CVD event-free survival, whereas there was no difference seen with stratification by LDL-C [22].

Given the data suggesting a particular role for small LDL particles in CVD, and the epidemiological observation of the "atherogenic lipoprotein phenotype" of increased small LDL particle numbers, decreased HDL-C, and increased triglycerides, some lipoprotein assays have defined cutoffs for LDL peak particle size, with high particle sizes designated as "pattern A" (normal; defined as >25.5 nm when measured by gradient gel electrophoresis [3]) and low particle sizes designated as "pattern B" (having an increased proportion of small LDL particles and, thus, more likely to have atherogenic dyslipidemia; defined as ≤ 25.5 nm when measured by gradient gel electrophoresis) to aid clinicians in categorizing patients at risk for CVD.

Principal Component Analysis of Lipoprotein Subfractions

Although numerous studies have demonstrated that some lipoprotein subfractions are predictive of CVD, none of these studies systematically analyzed the interrelationships among all of the various lipoprotein subfractions to determine whether there are distinct combinations of subfractions that independently confer cardiovascular risk. To address this question, we have applied the technique of principal component analysis to identify interrelated combinations of subfractions and determine their relationship

with CVD in a large prospective cohort study, the Malmö Diet and Cancer-Cardiovascular Cohort (MDC-CC) [23]. Principal component analysis is a statistical method that analyzes the interrelationships between numerous variables and yields a fewer number of components that explain most of the correlation information of the original variables. Each of the resulting components is an independent linear combination of the original variables; furthermore, the components are fully independent of one another, i.e., they have zero correlation.

When we applied principal component analysis to eleven lipoprotein subfractions measured by ion mobility analysis of samples from more than 4,500 individuals in MDC-CC, we identified three major independent components, all of which were associated with incident CVD in the cohort [23, 24]. Notably, one of the three components represented a pattern of increased small and medium LDL particle concentrations, decreased large HDL particle concentrations, and increased triglycerides—corresponding to atherogenic dyslipidemia. This component was much more highly associated with incident CVD events (hazard ratio of 1.22 per 1 standard deviation) than LDL-C (hazard ratio of 1.10 per 1 standard deviation), indicating it to be a superior predictor of disease [23]. The other two principal components represented LDL-associated CVD risk (hazard ratio of 1.10 per 1 standard deviation) and HDL-associated CVD protection (hazard ratio of 0.81 per 1 standard deviation). Thus, our analysis established that atherogenic dyslipidemia is an epidemiologically distinct risk factor for CVD than the traditional risk factors of LDL-C and HDL-C and represents an independent mechanistic pathway contributing to the pathogenesis of CVD. Accordingly, there is a strong rationale to explore genetic and dietary modifiers of this pathway in order to better craft targeted interventions to reduce CVD risk.

Genetics and Atherogenic Dyslipidemia

Family-based segregation analyses suggest that the atherogenic lipoprotein phenotype has a strong genetic basis that likely reflects contributions from numerous genes [14, 25, 26]. Candidate genes include those that influence LDL peak particle size; family-based and twin studies indicate a large heritable component of LDL size, ranging from 40 to 60% of the trait. Genes with variants that have been reported to be associated with LDL size include: *CETP*, encoding cholesteryl ester transfer protein, which exchanges cholesteryl esters and triglycerides from HDL lipoprotein particles to LDL particles; *LDLR*, encoding the LDL receptor, which is responsible for cellular uptake of LDL particles from the bloodstream; *LPL*, encoding lipoprotein lipase, which hydrolyzes triglycerides in chylomicrons and VLDL particles, converting the latter to LDL particles, as well facilitating cellular lipoprotein uptake; *MTP*, encoding microsomal triglyceride transfer protein, which transfers triglycerides to nascent VLDL particles in hepatocytes; and the apolipoprotein genes *APOA5*, *APOB*, *APOC3*, and *APOE*, which are important constituents of varied lipoprotein particles [25–35]. All of these genes play credible roles in determining the size and lipid content of LDL particles as well as other lipoprotein particles and so might directly contribute to atherogenic dyslipidemia.

By applying principal component analysis in the MDC-CC, we were able to define a component representing atherogenic dyslipidemia. This enabled us to perform genetic analyses on this specific component and thereby identify gene variants directly linked to the dyslipidemia profile, rather than a property of an individual lipoprotein (such as LDL size). We took advantage of data from a recent genome-wide association study on lipid traits, which identified 30 genetic loci strongly linked to one or more of the blood LDL-C, HDL-C, and triglyceride levels [36]. We assessed the strength of association between SNPs in each of these genetic loci and the atherogenic dyslipidemia component. We found that variants in six loci, harboring the *CETP*, *LPL*, *APOA5*, *LIPC*, *GALNT2*, and *MLXIPL* genes, were highly associated with this component. In confirmation, each of the SNPs at these genes was also associated with small/medium LDL particle concentrations and—in the opposite direction—large HDL particle concentrations as well as HDL-C and/or triglycerides [23]. Interestingly, the variants at all but two of the six genes (*CETP* and *APOA5*) were not associated with LDL-C.

Thus, the MDC-CC study validated several of the genes previously linked to LDL size as also having variants associated with atherogenic dyslipidemia, as well as identifying a few novel candidate genes. The implicated genes may interact in biological pathways that regulate the different components of the dyslipidemia profile; conceivably, interventions targeting one or more of these specific genes may modulate an individual's lipid/lipoprotein profile in a clinically favorable way and reduce the risk of CVD, even if they do not affect blood LDL-C levels.

Effects of Diet on Atherogenic Dyslipidemia

An important question is whether alterations in diet—whether in regard to carbohydrate, fat, or saturated fat content—have predictable effects on lipoprotein profiles and, specifically, atherogenic dyslipidemia. This has implications for nutritional counseling for patients at risk for CVD: which diets are likely to induce or worsen atherogenic dyslipidemia and thereby increase CVD risk, and

thus should be avoided, and which diets may reverse the dyslipidemia and should be recommended. A related question is whether particular diets are of greater or less benefit in individuals with atherogenic dyslipidemia compared to those without it.

In one study, 105 healthy middle-age men were placed on high-fat (46% of calories from fat), low-carbohydrate and low-fat (24% of calories from fat), high-carbohydrate diets in a crossover design in which they experienced 6 weeks on each diet [37]. To simplify the interpretation of the study results, the proportions of types of fat (unsaturated vs. saturated, 1:1 ratio) and types of carbohydrates (simple vs. complex, 1:1) remained fixed in these diets. Across all subjects, there were significantly higher levels of triglycerides and the LDL3/LDL4 subfractions (small and very small LDL particle concentrations), as well as lower HDL-C levels, while on the low-fat diet compared to the high-fat diet. Thirty-six subjects who were pattern A or intermediate (as judged by LDL peak particle diameter) when on the high-fat diet converted to pattern B on the low-fat diet; all of the individuals who were pattern B on the high-fat diet remained pattern B on the low-fat diet. In a follow-up study, the individuals who had been pattern A on both the high-fat and low-fat diets were subjected to a very-low-fat diet (10% of calories from fat, with replacement by carbohydrates) [38]. One-third of the subjects converted to pattern B on this diet. Thus, reduction of fat along with increased carbohydrate intake altered lipoprotein profiles towards atherogenic dyslipidemia.

Of interest, individuals who were pattern B on a high-fat diet, when compared to those who were pattern A on a high-fat diet, experienced a much larger reduction in LDL-C when on a low-fat diet [37]. This was confirmed in both men and in pre-menopausal women, with a two- to threefold greater reduction in LDL-C observed [39, 40]. This phenomenon appeared to be the consequence of differential effects on lipoprotein profiles. Pattern A individuals experienced a larger decrease in LDL1 (large LDL particle concentrations) and an increase in LDL3 (small LDL particle concentrations) with little change in LDL2 (medium-large particle concentrations), whereas pattern B individuals displayed a decrease in LDL2 with a smaller decrease in LDL1 and no change in LDL3. Besides explaining the discrepancy in LDL-C alteration, these observations also explain why many pattern A individuals converted to pattern B (35%) but not vice versa (6%).

Extrapolating across all of these studies, the prevalence of pattern B increases with the amount of dietary carbohydrate and decreases with the amount of dietary fat. However, in these studies the changes in the proportions of calories derived from fat were largely balanced by reciprocal changes in calories from carbohydrates, making it difficult to determine whether dietary fat or carbohydrates are the major influence on atherogenic dyslipidemia. A study in 178 overweight men shed some light on this question. When compared on a higher-carbohydrate diet (54% of calories from carbohydrates, 1:1 simple:complex) versus a lower-carbohydrate diet (39% of calories from carbohydrates, 1:1 simple:complex), between which the difference was made up of protein calories (15 vs. 29%) rather than fat (minimal change), the subjects had a higher prevalence of pattern B when on the higher-carbohydrate diet [41]. This observation suggests that dietary carbohydrates are the principal driver of atherogenic dyslipidemia.

A more complete analysis with the 178 overweight men was highly informative as to the effects of varying carbohydrates and saturated fat, as well as weight loss, on lipoprotein profiles [42]. Four diets were compared: (1) 54% of calories from carbohydrates (1:1 simple:complex) with low saturated fat, (2) 39% of calories from carbohydrates (1:1 simple:complex) with low saturated fat, (3) 26% of calories from carbohydrates (1:1 simple:complex) with low saturated fat, and (4) 26% of calories from carbohydrates (1:1 simple:complex) with high saturated fat. Diets (1) and (2) had equal fat content, diets (3) and (4) had equal fat content that was higher than that of diets (1) and (2). The subjects underwent a weight-maintenance phase of 3 weeks on the assigned diets, followed by a weight-loss phase of 5 weeks (with a subsequent four-week weight stabilization period) on the same diets.

During the weight-maintenance phase, the subjects on the low-carbohydrate diets [(3) and (4)] experienced significant decreases in their triglyceride levels as well as their LDL3 and LDL4 levels (small and very small LDL particle concentrations); the individuals on the higher-carbohydrate diets displayed only modest changes. In contrast, during the weight-loss phase, the individuals on higher-carbohydrate diets experienced larger decreases in triglycerides and small LDL particle concentrations than did those on low-carbohydrate diets. Thus, by the end of the study, the higher-carbohydrate subjects had "caught up" with the low-carbohydrate subjects. The lower the dietary carbohydrate content, the lower the prevalence of pattern B, both after the weight-maintenance phase and after the weight-loss phase, although the differences in the prevalence of pattern B were smaller after weight loss, again pointing to a "catch-up" phenomenon.

Comparing the low-saturated-fat and high-saturated-fat low-carbohydrate diets [(3) vs. (4)], there were essentially no differences in changes in triglycerides, small LDL particle concentrations, or prevalence of pattern B, either in the weight-maintenance or weight-loss phases [42]. This finding indicates that dietary saturated fat content has little influence on the components of the atherogenic lipoprotein phenotype. This agrees with the results of a study that compared the effects of four-week treatments with a

high-saturated-fat diet (38% of calories from fat, with 20% of calories from saturated fat), a monounsaturated fatty acid (MUFA) olive oil-rich diet (38% of calories from fat, with 22% of calories from MUFA), and a high-carbohydrate diet (30% of calories from fat, with <10% of calories from saturated fat, and 55% of calories from carbohydrates) in 84 individuals [43]. (In all diets, ~40% of the carbohydrate calories came from simple carbohydrates, the remainder from complex carbohydrates.) There were no differences in triglycerides, LDL size, or prevalence of pattern B between the high-saturated-fat and high-MUFA diets; in contrast, both high-fat diets yielded higher LDL sizes than the high-carbohydrate diet, with one-third of the subjects converting from pattern A to pattern B with the high-carbohydrate diet. The lack of difference in LDL size seen between the two high-fat diets is consistent with two earlier studies, one of which noted a minimal increase in LDL size with a high-MUFA diet compared to a high-saturated-fat diet [44], the other of which reported no difference [45].

Finally, analysis of a prospective cohort study (the Framingham Heart Study) confirmed that fat content in the diet, after multivariable adjustment for carbohydrate intake and a variety of other potential confounders, did not significantly affect LDL size or triglyceride levels in either men or women [46]. This was true regardless of the quality of fat studied—total fat, saturated fat, MUFA, or polyunsaturated fatty acid (PUFA) content. Thus, it appears that both the quantity and quality of fat consumed (assuming no change in the number of calories obtained from carbohydrates) have minimal effects on the atherogenic lipoprotein phenotype.

Although it is possible that different types of carbohydrates may have different effects on lipoproteins, none of the discussed studies were able to shed light on this question, since in all cases the ratio of simple to complex carbohydrates was kept constant among the experimental diets. Given that carbohydrate intake appears to be the primary driver of atherogenic dyslipidemia, it would be desirable for future studies to directly compare diets in which the proportions of different types of carbohydrates are varied, with the overall number of calories coming from carbohydrates being held constant.

In conclusion, either lowering the dietary carbohydrate content or losing weight appears to attenuate atherogenic dyslipidemia (although there does not appear to be an additive effect of the two), whereas altering the total fat or saturated fat content has little influence. However, being placed on a lower-fat, higher-carbohydrate diet appears to result in lower LDL-C levels than a higher-fat, lower-carbohydrate diet, particularly for individuals starting with pattern B. Thus, it remains unclear whether having high or low dietary carbohydrate content is more beneficial for cardiovascular health. It should be noted that the intervention studies described above were all short-term (weeks) and so were not able to compare long-term CVD outcomes resulting from the various diets. Thus, we await long-term studies before these data can be used to help shape nutritional recommendations for patients at CVD risk.

Interactions of Genetics and Dietary Interventions

Given that both genetics and diet contribute to the atherogenic lipoprotein phenotype, it is natural to expect that there may be interactions between the two factors. For example, individuals with specific variants in a gene may experience changes in lipoprotein concentrations when placed on a particular diet, whereas individuals with other variants in the gene may be resistant to the effects of that diet. Another possibility is that individuals with one set of genetic variants may experience different types of lipoprotein changes than individuals with a different set of genetic variants, when all are placed on the same diet. This might manifest, for instance, as some individuals being more prone than others to developing atherogenic dyslipidemia on a high-carbohydrate diet. Although data is sparse in regard to whether such interactions exist, some limited work suggests that interactions may play an important role in determining lipoprotein profiles and may thus be informative for CVD risk prediction. For example, knowledge of a patient's genetic information may allow medical providers and nutritional counselors to predict what lipoprotein changes are likely to occur if the patient starts a particular dietary intervention and, thus, better advise the patient regarding lifestyle changes.

In one study, 50 individuals with pattern A lipoprotein profiles, offspring of 29 sets of parents, were tested for induction of pattern B with a very-high-carbohydrate diet [47]. Notably, all six of the subjects who converted to pattern B were descended from two pattern B parents. Quantitatively, LDL peak particle size decreased to a greater degree in offspring of two pattern B parents than in offspring of two pattern A parents. These findings suggest that there is a heritable basis for the induction of atherogenic dyslipidemia by a carbohydrate-rich diet.

A more detailed study was performed to examine the interaction of varied dietary fat content and variation in the *APOA5* gene, one of the genes previously linked to atherogenic dyslipidemia [39, 48]. An uncommon DNA sequence variant in *APOA5* (~6% frequency in individuals of European descent) that alters the 19th amino acid of the apoA-V protein from serine to tryptophan, termed *APOA5*3*, was compared to the usual variant at the DNA base, termed *APOA5*1*. Individuals who had a genotype of

*1/*3 (one of each variant), when compared to individuals with *1/*1 (two copies of the usual variant) had higher small LDL particle concentrations and triglycerides, as well as higher prevalence of pattern B, regardless of whether they were on a low-fat or high-fat diet. Also, there were higher small LDL particle concentrations and triglycerides and higher prevalence of pattern B when comparing all individuals on a low-fat diet compared to those on a high-fat diet. However, there were no differences in the relative changes of small LDL particle concentrations and triglycerides—or relative rates of pattern B—between *1/*3 and *1/*1 individuals on low-fat versus high-fat diets.

Thus, while both the *3 allele and, separately, a low-fat diet influenced the lipoprotein profile towards atherogenic dyslipidemia, there was no evidence for an interaction between genotype and diet. Interestingly, the only significant difference seen in the relative changes of lipoproteins between the two genotype groups on fat-varied diets was with the LDL2 subfraction (corresponding to medium-large LDL particle concentrations), where *1/*3 subjects experienced a threefold greater decrease in LDL2 than *1/*1 subjects when on a low-fat diet versus a high-fat diet [39]. Thus, *APOA5* did not appear to affect dietary induction of atherogenic dyslipidemia, though it did modulate dietary effects on some lipoproteins.

A somewhat different analysis in the Framingham Heart Study examined both the *APOA5*3* variant as well as a different variant that alters a DNA base in the *APOA5* promoter (–1131T > C, termed *APOA5*2*) with respect to potential interactions with dietary fat intake in modulating lipoproteins [46]. Individuals with the *APOA5*2* variant displayed increased triglycerides and smaller LDL size when the dietary PUFA content was >6% (by calories); individuals without the variant showed no differences with varied PUFA intake. There were no interactions of the *APOA5*2* variant with total fat, saturated fat, or MUFA intake, nor were there any interactions of the *APOA5*3* variant with any type of fat.

Thus, while both of the *APOA5* studies discussed here suggest that *APOA5* does influence the dietary effects of fat intake on lipoproteins, they disagree on the effects of specific gene variants. This highlights a critical problem in the study of gene-diet interactions, the lack of consistency between studies. In this example, the two studies differed in study design (one was a short-term interventional study, the other an observational prospective cohort study), the types of diets examined (one focused only on total fat intake, the other on total fat as well as specific types of fat), the variants examined (one focused only on *APOA5*3*, the other on both *APOA5*2* and *APOA5*3*), the measurement of lipoproteins (one assessed each of the LDL subfractions, the other only LDL size), and the populations studied (one focused on overweight men, the other on a population-based sample).

As such, it is difficult to draw any firm conclusions from any one gene-diet study in the absence of replication by another study that examined the same question using similar methodologies. For example, one study demonstrated that a Mediterranean-style, MUFA-rich diet compared to a high-carbohydrate diet increased LDL size in individuals with certain *APOE* gene variants but decreased LDL size in those with other *APOE* variants; [43] this is potentially a clinically important observation, but no confirmatory study has yet emerged, calling this observation into doubt. As pointed out by others, the field would greatly benefit from increased collaboration and coordination of studies among international nutrition researchers [49].

Conclusion

Atherogenic dyslipidemia appears to be an important independent risk factor for CVD, confirmed by principal component analysis of lipoprotein subfractions in a large prospective cohort study. As the genetic basis of lipoprotein metabolism becomes better understood, gene variants contributing to atherogenic dyslipidemia are being identified; these genes may serve as therapeutic targets to modulate the adverse effects of the dyslipidemia. It is clear that either reduction of dietary carbohydrate content or weight loss will improve an atherogenic dyslipidemic profile, whereas specifically altering fat or saturated fat content may have little influence. We await long-term clinical trials to assess whether genetic and/or dietary interventions with the intent of modifying the dyslipidemia will ultimately translate into reduction of CVD risk.

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