Influence of Dietary Carbohydrate and Fat on LDL and HDL Particle Distributions

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Variations in the size and density distributions of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles have been related to risk for cardiovascular disease. In particular, increased levels of small, dense LDL particles, together with reduced levels of large HDL and increases in small HDL, are integral features of the atherogenic dyslipidemia found in patients with insulin resistance, obesity, and metabolic syndrome. Increased dietary carbohydrates, particularly simple sugars and starches with high glycemic index, can increase levels of small, dense LDL and HDL, primarily by mechanisms that involve increasing plasma triglyceride concentrations. Low-carbohydrate diets may have the opposite effects. Diets with differing fatty acid composition can also influence LDL and HDL particle distributions.

Introduction

Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles are comprised of a heterogeneous array of particles that have distinctive metabolic behaviors and pathologic roles [1•]. The diversity of these populations can arise from differential catabolic pathways of precursor particles, metabolic remodeling, and direct production. In general, LDL and HDL particles that are smaller and denser have been associated with increased cardiovascular disease risk.

A common lipid and lipoprotein phenotype that has been associated with increased coronary heart disease risk includes increased triglyceride concentrations, reduced HDL cholesterol, and increased concentrations of small, dense LDL, with variable increases in total LDL cholesterol [2]. This constellation of risk factors, which is also closely linked with insulin resistance and excess adiposity, has been termed atherogenic dyslipidemia [3] or atherogenic lipoprotein phenotype [4].

Elevated concentrations of plasma triglyceride may form the basis of the lipid profile of reduced HDL cholesterol and smaller and more dense LDL by driving the secretion of apolipoprotein (apo)B-containing particles from the liver and by promoting intravascular remodeling of LDL and HDL. Lipoprotein particles secreted from the liver with excess triglyceride are more susceptible to lipoprotein lipase–mediated lipolysis as well as exchange of triglyceride for HDL cholesterol through the actions of the enzyme cholesterol ester transfer protein. The substrate-driven increase in lipolysis of the triglyceride contained within apoB-containing lipoprotein particles that comprise a metabolic cascade (*ie*, very low-density lipoprotein [VLDL], intermediate-density lipoprotein, and LDL) can result in the production of LDL particles that are smaller and more dense [1]. Plasma VLDL concentrations have been shown to correlate well with increased density and decreased size of LDL [5,6].

The formation of HDL begins with the secretion of lipid-poor apoA-I into the vasculature, where additional phospholipids and cholesterol are acquired onto the particles through cellular efflux and transfer from triglyceride-rich, apoB-containing lipoproteins [7•]. Subsequent intravascular maturation and remodeling through cholesterol esterification, lipid exchange, and triglyceride lipolysis result in the formation of a heterogeneous HDL population. As with LDL, triglyceride enrichment of HDL, which occurs with increases in plasma levels of triglyceride, provides substrate for lipolysis by hepatic lipase, resulting in particles that are smaller, less stable, and more susceptible to catabolism [8,9]. In vivo lipoprotein-turnover studies in humans have reported increased catabolic rates of apoA-I in hypertriglyceridemic persons with reduced HDL cholesterol concentrations compared with normolipidemic persons [10–12]. Recently, however, apoA-I levels in obesity have been found to be associated primarily with apoA-I production rate [13•].

Heterogeneity of LDL and HDL Particles

There are seven distinct species of LDL, divided into four subclasses denoted LDL-I to LDL-IV, signifying particles that range from larger and more buoyant particles to ones that are smaller and more dense [1•]. These subspecies of LDL have been shown to vary in lipid and carbohydrate composition [14] as well as in conformation of apoB [15,16]. Importantly, the residence time of small, dense LDL in plasma may be prolonged given their relatively reduced affinity for the LDL receptor [15,17,18]. Other intrinsic physicochemical and metabolic properties of small, dense LDL that may contribute to their atherogenicity include their greater propensity for transport into the subendothelial space [19], increased binding to arterial wall proteoglycans, and increased susceptibility to oxidative modification [20].

HDL particles also vary in diameter and density, with HDL_{3a}, HDL_{3b}, and HDL_{3c} comprising particles that are smaller and more dense, and HDL_{2a} and HDL_{2b} comprising the larger and more buoyant HDL particles [21]. Typically, the reduced level of HDL cholesterol in atherogenic dyslipidemia is associated with lower levels of larger HDL_2 particles, a relative increase in smaller HDL_3, and a shift to lower peak HDL particle diameter [22–24]. Smaller and more dense LDL particles have been inversely associated with concentrations of the larger and more buoyant subclass of HDL [25].

High-carbohydrate, Low-fat Diets Can Increase Small, Dense LDL and HDL

The prevalence of "pattern B," the phenotype of small, dense LDL, has been well correlated with average dietary fat intake in cross-sectional population studies. In the United States, where the average fat intake is approximately 34% of energy, the prevalence of pattern B is in the range of 30% to 35%. In rural Costa Rica, where fat intake is lower, the prevalence of pattern B is higher [26].

Intervention studies by our group and others [27–29] have also shown that in conjunction with the well-known increase in plasma triglyceride produced by diets low in fat and high in carbohydrate [30], such diets also lead to increased concentrations of small, dense LDL and reduced HDL cholesterol. Significant inter-individual variation in the response to altered dietary composition has been observed [31,32], and these differences have been attributed at least in part to genetics [31,33]. Kinetic studies have been used to demonstrate that the hypertriglyceridemic effects of high dietary carbohydrate occur primarily due to decreased clearance of apoB-containing particles [34] associated with decreased lipoprotein lipase activity and/or decreased concentrations of apoC-III. There is also evidence that fatty acid synthesis and triglyceride secretion can be increased by high carbohydrate feeding [35].

Replacement of dietary fat with carbohydrate has been shown to lead to unfavorable changes in HDL, with significant decreases in HDL_{3a}, HDL_{2a}, and HDL_{2b} [22]. Although the mechanism by which dietary carbohydrate affects HDL particle size remains unclear, turnover studies in humans have shown that the response of HDL cholesterol to diet is mediated by changes in overall flux or transport rates as opposed to fractional clearance rates [36].

Interestingly, high-carbohydrate diets, when consumed ad libitum, may promote weight loss, leading to reduced concentrations of smaller and more dense LDL and HDL particles [37,38]. These improvements are more likely a function of weight loss than composition of diet; recent studies from our group have also demonstrated the more potent effects of weight loss over diet composition in the determination of the prevalence of pattern B [39].

Although quantity of carbohydrate is important in the determination of lipid and lipoprotein parameters, it is well established that the nature of dietary carbohydrates, expressed for example in terms of their ability to raise blood glucose or glycemic index, can markedly affect plasma triglyceride and related metabolic variables [30,40]. A low-glycemic index, low-fat diet has been reported to improve components of atherogenic lipoprotein phenotype in a short-term study of 12 obese men [41]. Recently, the consumption of high-glycemic index foods as assessed by 3-day food diaries was shown to be inversely associated with HDL cholesterol levels in a population of adolescents and young adults [42•]. Similarly, a high-glycemic index compared with a low-glycemic index diet was shown to be associated with reduced HDL cholesterol in a randomized controlled trial of 21 patients with type 2 diabetes [43]; however, no associations with HDL or LDL particle size were observed.

Effects of Dietary Fat on LDL and HDL Heterogeneity

Diets with varying carbohydrate content are usually defined by reciprocal variation in fat. Thus, generally speaking, the effects of low-fat diets on lipid and lipoprotein parameters are similar to the effects described previously for high-carbohydrate diets (*ie*, low-fat diets increase plasma triglyceride and decrease HDL cholesterol levels) [37,44,45]. These lipid changes are less pronounced or can even be completely ameliorated when the low-fat diet is associated with weight loss [37,38,45].

As with carbohydrates, the quality of dietary fat may play a role in the determination of LDL and HDL heterogeneity. Types of fats include saturated, monounsaturated, and polyunsaturated fat as well as omega-3 and trans fatty acids. Relative to carbohydrates, saturated, monounsaturated, and polyunsaturated fats have been shown to lower triglycerides [46] and raise HDL cholesterol, an effect diminished with increasing unsaturation of the fatty acids [47].