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Original Article

Lifestyle intervention enhances high-density lipoprotein function among patients with metabolic syndrome only at normal low-density lipoprotein cholesterol plasma levels

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KEYWORDS:
Metabolic syndrome;
High-density lipoprotein;
Antioxidative activity;
Oxidative stress;
Lifestyle intervention

BACKGROUND: Metabolic syndrome (MetS) is associated with altered lipoprotein metabolism and impairment in the functionality of small, dense high-density lipoprotein (HDL) particles secondary to compositional alterations.

OBJECTIVE: The objective of this study was to investigate the capacity of a lifestyle program to improve the composition and antioxidative function (AOX) of small dense HDL3c in MetS.

METHODS: Patients with MetS (n = 33) not taking lipid-lowering drugs were recruited to follow a 12-week educational program to reduce caloric intake and to increase physical activity. HDL subfractions were preparatively isolated by isopycnic density-gradient ultracentrifugation. AOX of HDL3c was assessed as its capacity to inhibit low-density lipoprotein oxidation induced by an azoinitiator.

RESULTS: AOX of HDL3c was significantly improved (mean reduction in the propagation rate of low-density lipoprotein oxidation by HDL3c, −6.8%, $P = .03$) and systemic oxidative stress, assessed as plasma levels of 8-isoprostanes, tended to decrease in normocholesterolemic MetS patients (low-density lipoprotein cholesterol [LDL-C] < 130 mg/dL) but not in patients with elevated LDL-C levels and in the whole study population. In both the whole study population and the normocholesterolemic subgroup, lifestyle intervention resulted in a significant degree of normalization of HDL3c

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composition, (enrichment in apolipoprotein A-I and cholesteryl esters, depletion in triglycerides), which was more pronounced at LDL-C < 130 mg/dL.

CONCLUSION: In patients with MetS, a lifestyle program improves AOX of small, dense HDL in subjects with normal LDL-C levels. Correction of HDL composition, involving partial normalization of apoA-I content and core lipid composition, 2 central features of the lipid hydroperoxide-inactivating capacity of HDL, may account for this effect.

Introduction

Metabolic syndrome (MetS) is characterized by a constellation of cardiovascular (CV) risk factors, including atherogenic dyslipidemia, abnormal glucose tolerance, hypertension, and visceral obesity, which are intimately associated with insulin resistance and hyperinsulinemia.

Lipid abnormalities associated with MetS typically include high plasma levels of triglycerides (TGs) and low levels of high-density lipoprotein cholesterol (HDL-C). In addition, MetS is associated with altered profiles of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) subfractions characterized by increased proportions of dysfunctional small, dense, LDL, and HDL particles.[1,2] Such alterations in lipoprotein subfraction distribution reflect metabolic perturbations associated with insulin resistance and accumulation of visceral fat, which result in enrichment of LDL and HDL particles in TG with concomitant depletion in cholesterol. Such metabolic alterations are in large part due to elevated activity of cholesteryl ester transfer protein (CETP) in the presence of elevated levels of TG-rich lipoprotein acceptors[3]; indeed, CETP mediates the transfer of cholesteryl esters (CEs) from HDL to proatherogenic apoB-lipoproteins, with heterotransfer of TG mainly from very low–density lipoprotein (VLDL) to HDL.[3] Such compositional modifications are accompanied by marked alterations in the biological function of the lipoproteins.[4] On the one hand, the preponderance of small, dense LDL particles, which are highly susceptible to oxidative modification, increases the overall oxidizability of the circulating LDL pool. On the other hand, the capacity of HDL, and primarily of potently antioxidative, small, dense HDL3c particles to protect LDL from oxidation, is deficient among patients with MetS[5] and equally among patients with type 2 diabetes[6] and in those with isolated low HDL-C levels.[7] Importantly, under these conditions, the antioxidative activity of HDL3c was negatively correlated with elevated systemic oxidative stress, which was itself quantified as plasma concentrations of 8-isoprostanes and oxidized LDL (oxLDL), 2 biological markers known to be associated with CV disease.[8]

Although the results of the VA-HIT Study[9] and Helsinki Heart Study[10] have shown that increasing levels of HDL-C and lowering those of TGs and non–HDL-C with gemfibrozil reduce risk of coronary heart disease in patients not taking statins, recent trials of agents aimed specifically to increase HDL-C (including CETP inhibitors) have failed to confer protection against CV disease in patients under statin therapy. One possible explanation for such negative results involves the lack of beneficial effects conferred by HDL-targeting drugs on the antiatherogenic function of HDL despite their positive effects on HDL-C levels. Indeed, a recent metaregression analysis by Hourcade-Potelleret et al[11] suggests that the use of HDL-C as a surrogate marker of coronary events associated with abnormalities of HDL metabolism is not sufficient and that markers of HDL function may be more relevant. To reduce CV risk among patients with high levels of TG-rich lipoproteins and low plasma HDL-C levels, the European Atherosclerosis Society Consensus Panel recommends lifestyle modifications as the first step in therapeutic intervention.[11] Indeed, despite a relatively weak impact on HDL-C levels,[12,13] lifestyle modifications aimed at increasing physical activity and improving nutritional habits may reduce CV risk even in the absence of major alterations of traditional CV risk factors.[14]

We hypothesize that beneficial effects of lifestyle modifications might be partially related to enhanced function of defective HDL particles. So far, few studies have examined the effect of lifestyle changes and/or weight loss on the antiatherosclerotic function of HDL particles.[15–18] In a follow-up of our initial studies, which documented impaired antioxidative and antiapoptotic activities of small, dense HDL in MetS, we assessed the effect of weight loss induced by diet and exercise on the subfraction profile of plasma HDL particles, on the antioxidative function (AOX) of small, dense HDL3c and on biological markers of oxidative stress. Due to the heterogeneity of our population including both patients with high and desirable low-density lipoprotein cholesterol (LDL-C) plasma levels, we decided *a priori* to stratify analyses by LDL-C levels choosing the cutoff proposed by NCEP-ATP III to Q4 distinguish optimal to above optimal values and borderline to very high values.[19]

Material and methods

Subjects

A total of 33 consecutive subjects (25 men and 8 women) were recruited at the Cardiovascular Prevention Unit of the Hopital La Pitié-Salpêtrière (Paris, France)