

Obesity-related Changes in High-density Lipoprotein Metabolism

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Obesity is associated with a 3-or-more-fold increase in the risk of fatal and nonfatal myocardial infarction (1–6). The American Heart Association has reclassified obesity as a major, modifiable risk factor for coronary heart disease (7). The increased prevalence of premature coronary heart disease in obesity is attributed to multiple factors (8–10). A principal contributor to this serious morbidity is the alterations in plasma lipid and lipoprotein levels. The dyslipidemia of obesity is commonly manifested as high plasma triglyceride levels, low high-density lipoprotein cholesterol (HDLc), and normal low-density lipoprotein cholesterol (LDLc) with preponderance of small dense LDL particles (7–10). However, there is a considerable heterogeneity of plasma lipid profile in overweight and obese people. The precise cause of this heterogeneity is not entirely clear but has been partly attributed to the degree of visceral adiposity and insulin resistance. The emergence of glucose intolerance or a genetic predisposition to familial combined hyperlipidemia will further modify the plasma lipid phenotype in obese people (11–15).

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The major lipoprotein constituents of HDL are apolipoprotein A-I (apo A-I) and apo A-II. Whereas apo A-I has cardioprotective properties, apo A-II has been associated with increased risk of atherosclerosis in animal models (16,17). Metabolic and nutritional correlates of obesity commonly alter the production of apo A-I and other lipoproteins.

In this review, the obesity-related changes in HDL metabolism will be reviewed and the potential mechanisms contributing to these changes will be discussed. The direct and indirect effects of interventions targeting body weight reduction will also be discussed briefly.

BIOLOGICAL FUNCTIONS OF HDL AND ITS APOLIPOPROTEINS

Heterogeneity of HDL can be categorized either based on its lipid composition, a major determinant of its size and density, or based on apoprotein composition. HDL₂, HDL₃ and pre-βHDL represent the largest most buoyant to smaller and denser HDL particles, respectively (16–18). The other categorization of HDL

based on apoprotein content identifies the HDL that is mostly apo A-I or a mixture of apo A-I and apo A-II, referred to as LpA-I and the LpA-I:A-II, respectively. Additional minor apolipoprotein components of HDL are apo Cs (i.e., C-I, C-II, and C-III) and apo E. The latter is a ligand for hepatic LDL and apo E receptors and mediates the uptake of a subgroup of HDL particles such as HDL₁. Apo C-I is an activator of lecithin-cholesterol acyltransferase (LCAT), apo C-II activates lipoprotein lipase (LPL), and apo C-III is an inhibitor of hepatic lipase (HL) (18).

Although HDL₂ is considered more cardioprotective than HDL₃, there remains considerable uncertainty regarding the role of each HDL species. Similarly, the role of apo A-II in promoting or inhibiting cholesterol efflux is also controversial. The potential deleterious effects of apo A-II include inhibition of LCAT and hepatic cholesterol uptake through its effects on scavenger receptor class B type 1 receptor (18). However, apo A-II also has potential beneficial effects such as inhibition of cholesteryl-ester

transfer protein (CETP) and increasing HL activity (18).

The cardioprotective effects of HDLc and apo A-I have been attributed to multiple mechanisms (16–18). These mechanisms will be discussed briefly.

Reverse cholesterol transport

At the present time, reverse cholesterol transport (RCT) is considered to be the principal mechanism by which HDL decelerates atherosclerotic process (16–18). A schematic diagram showing the major steps in the RCT is shown in **Figure 1**. The process starts when the nascent HDL particle composed mostly of apo A-I takes up the cholesterol that is exported from target tissues either by diffusion or more importantly through the action of ATP-binding cassette transporter A1 (**Figure 1**). Subsequently, the free cholesterol is esterified by LCAT, and the HDL particle changes in geometry from discoidal to spherical in shape. The spherical HDL, namely HDL₃, continues to grow forming HDL₂ by accepting additional cholesterol. The HDL₂ transfers

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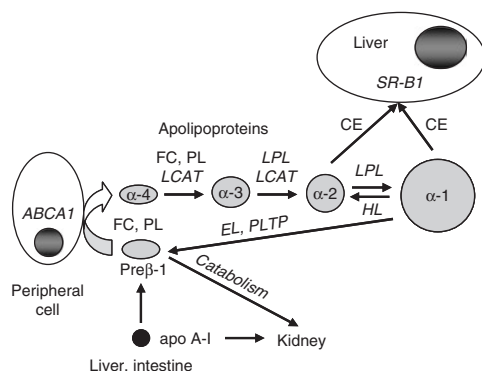


Figure 1 Reverse cholesterol transport and high-density lipoprotein (HDL) metabolism. Phospholipid (PL) and free-cholesterol (FC) are taken up by pre β -1 HDL utilizing the transporter ATP-binding cassette protein A1 (ABCA1) to form HDL $_{\alpha-4}$. FC is converted to cholesterol ester (CE) by lecithin-cholesterol acyltransferase (LCAT), lipids are released by lipoprotein lipase (LPL) and hepatic lipase (HL), and the HDL is converted to larger, less-dense lipoproteins forming HDL $_{\alpha-2}$ and HDL $_{\alpha-1}$. CE is taken up by liver parenchymal cells via scavenger receptor-B1 (SR-B1). Both free-apolipoprotein A-I (apo A-I) and pre β -1 HDL are catabolized in the kidney after binding to the cubulin receptor. EL, endothelial lipase; PLTP, phospholipids transfer protein.

cholesterol to other lipoproteins such as LDL and the very LDL (VLDL) through the CETP or accepts free cholesterol and phospholipids from hydrolysis of VLDL mediated by LPL and facilitated by phospholipid transfer protein (PLTP). Cholesterol transferred off the HDL $_2$ is replaced by triglycerides. The hydrolysis of this triglyceride by HL and the hydrolysis of phospholipids by endothelial lipase accelerate the renal clearance of the apo A-I by cubulin, an endocytic receptor. The cholesterol ester in the hydrophobic core of the HDL particle is taken up in the liver through the scavenger receptor class B type 1 receptor. The apo A-I that is released either re-enters the RCT cycle or undergoes metabolic degradation or renal clearance.

It is noteworthy that the level of HDLc does not predict the efficiency of RCT or the cardio-protectiveness of HDL. Thus, inhibition of CETP and the attendant increase in HDLc level failed to reduce cardiovascular events (19). In addition, a common CETP promoter polymorphism which leads to a significant decrease in CETP gene transcription and thereby leading to higher HDLc levels is paradoxically associated with increased incidence of coronary disease (20). These observations underscore the importance of understanding the metabolic pathway regulating HDLc as a determinant of its effects on coronary artery disease.

Other atheroprotective mechanisms

One of the principal properties of HDL that imparts cardioprotective function is that it has antioxidant activity. This has been demonstrated by the ability of HDL to bind transition metals, and its association with two enzymes, namely paraoxonase and platelet activating factor-acylhydrolase (16–18).

Another important cardioprotective feature of HDL is its anti-inflammatory activity. This could be partly related to its antioxidative potential or to its ability to increase intracellular ceramide through inhibition of sphingosine kinase (16–18). Recent proteomic analysis of HDL implicated protease inhibition and complement activation in the anti-inflammatory properties of HDL particle (21). Additional cardioprotective properties of HDL include scavenging toxic by-products of LDL oxidation such as lysophosphatidylcholine, antithrombotic and fibrinolytic activity through promotion of protein C, and inhibition of LDL retention through apo E-related effects. (For more detailed review of the topic, see refs. 16–18,22,23). The relative importance of each cardioprotective property of HDL is not known. It is noteworthy that *in vivo* modification of HDL may impair its function or render it proatherogenic (24,25). The concentration of HDLc may not reflect the true functional attributes of this lipoprotein.

EPIDEMIOLOGY OF LOW HDL IN OBESITY

Low HDLc is a common lipid disorder in obesity especially in the context of metabolic syndrome. The prevalence of this syndrome is high especially in certain ethnic groups (26–29). In a study of 8,814 men and women (>20 years old) participating in the Third National Health and Nutrition Examination Survey (NHANES III), there was 24% prevalence of metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) (27). The prevalence increases with age, and 33–45% of subjects >50 years meet the criteria for the metabolic syndrome (28). Among NHANES III participants with diabetes who were >50 years old, the prevalence of metabolic syndrome was 86.0%, while 26% of normoglycemic individuals had metabolic syndrome according to the NCEP definition (28). The most common component of the metabolic syndrome in US adults ≥ 20 years was obesity (39%) followed immediately by the low HDLc level (37%) (26,30).

The prevalence of low HDLc among overweight and obese individuals is variable. In obese people with a BMI > 30, the prevalence of low HDLc (<45 in women and <35 mg/dl in men) is 40.6% in women and 31.1% in men (31).

Low plasma HDLc level in obesity can occur in the presence or absence of hypertriglyceridemia. It is estimated that ~50% of obese people without hypertriglyceridemia have reduced HDLc (32). The pathophysiology of low HDLc in this large subgroup of individuals is probably distinct from those who have high plasma triglyceride levels.

EFFECT OF OBESITY ON HDL METABOLISM AND RCT

In obesity, the reduced plasma HDLc levels have been attributed to increased fractional clearance of HDL secondary to depletion of its cholesterol (33,34).

Several key enzymes involved in HDL metabolism are altered in obese people with insulin resistance (Table 1). Some of these changes are further accentuated in type 2 diabetes where in addition to insulin resistance, relative or absolute insulin deficiency may augment the abnormalities in RCT. Cellular cholesterol efflux

to normocholesterolemic normotriglyceridemic diabetic plasma is probably impaired, partly because of impaired actions of the cholesterol transporter ATP-binding cassette transporter A1 and scavenger receptor class B type 1 receptor.

However, the capacity of plasma to facilitate cholesterol efflux from cultured fibroblasts can be modulated by confounding variables that are commonly found in people with diabetes. Thus, cholesterol efflux to plasma may be increased in type 1 diabetic subjects with moderate hypercholesterolemia (35). Similarly, cholesterol efflux may be increased in type 2 diabetic subjects with hypertriglyceridemia with associated increased PLTP activity (36,37). PLTP promotes the formation of nascent pre-βHDL particles that are the initial acceptors of cell-derived cholesterol (36,37). Increased HDLc and apo A-I in the subset of type 1 diabetic subjects with hypercholesterolemia, and increased PLTP activity in those with hypertriglyceridemia, may effectively counteract the other diabetes-related changes that inhibit cholesterol efflux. Thus, cholesterol efflux studies should be interpreted in the light of overall plasma lipid profile and other risks of atherogenicity.

Insulin resistance is also associated with a decreased postheparin plasma LPL/HL ratio. This change contributes to the low HDLc levels in obesity because LPL activity promotes lipid availability for HDL while HL hydrolyzes the HDL triglyceride and phospholipids and renders the HDL particle more susceptible to metabolic clearance (33).

The LCAT-mediated esterification of cholesterol is either modestly increased or unaltered in obese subjects with insulin resistance while the CETP activity is increased. The latter change depletes HDL of its cholesterol and contributes to lowering of HDL levels. It is noteworthy that neither CETP nor PLTP activity is independently associated with insulin sensitivity, and PLTP activity is increased as a result of the association of plasma PLTP with plasma triglycerides (33). It is not known whether hepatic metabolism of HDL-derived cholesterol and subsequent hepatobiliary transport

is altered in insulin resistance or in type 2 diabetes (33).

An important metabolic trigger for reduced HDLc levels in obesity and insulin resistance is the increased VLDL production, at least partly because of increased fatty acid flux to the liver (14). This change promotes exchange of triglyceride for HDLc ester through the action of CETP. The triglyceride-enriched HDL is then hydrolyzed through HL or LPL, and apo A-I dissociates from smaller HDL, is filtered by the glomerulus, and degraded in renal tubular cells (17,18) (Figure 2). The relative importance of this pathway in individuals who do not have increased VLDL production or hypertriglyceridemia is not known. It appears that 50% of obese normotriglyceridemic individuals have low HDLc levels (32). In this population, the degree of adiposity and insulin resistance continues to be a major predictor of low HDLc. One potential cause is the inability of insulin to upregulate the apo A-I production in

those with insulin resistance (17,38,39). It is also possible that insulin resistance and low HDLc levels may have a common mediator such as tumor necrosis factor-α that is implicated in both obesity-related insulin resistance and is found to down-regulate the apo A-I gene expression and can lower serum HDLc levels (40,41). Serum leptin, adiponectin and highly sensitive C-reactive protein levels did not appear to be predictors of low HDLc levels in normotriglyceridemic obese individuals (32).

Heterogeneity of HDLc turnover in subjects with reduced concentrations of plasma HDLc was demonstrated previously by Le and Ginsburg (42). In the latter study, subjects with low HDLc without hypertriglyceridemia had significantly reduced HDLc production rate while the fractional clearance rate was not altered. The decreased HDLc production rate could be the result of either decreased apo A-I production or decreased cholesterol ester assembly

Table 1 Obesity or insulin resistance-related alterations in reverse cholesterol transport and HDL metabolism

I	Reduced efflux of cholesterol from peripheral cells; more pronounced in type 2 diabetes unless the plasma triglyceride level is high and PLTP activity is increased
II	Abnormal HDL remodeling
III	Unaltered esterification of cholesterol by LCAT
IV	Increased uptake of HDL cholesterol by SR-B1 possibly secondary to high HL activity
V	CETP mediated transfer of cholesterol to apo B containing lipoproteins may be increased

CETP, cholesteryl-ester transfer protein; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin-cholesterol acyltransferase; PLTP, phospholipid transfer protein; SR-B1, scavenger receptor-B1.

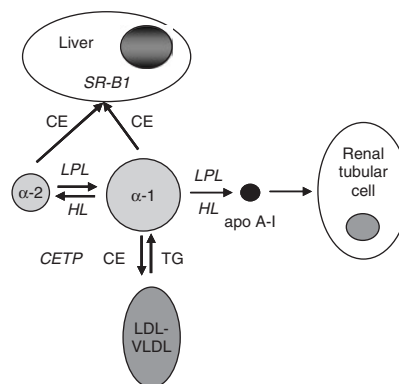


Figure 2 Remodeling of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) by cholesteryl-ester transfer protein (CETP). Cholesterol esters (CEs) are transferred to LDL from HDL_{α-1} (α-1) by the enzyme CETP in exchange for triglyceride (TG), changing the density of both lipoproteins. HDL can then be taken up by the liver or catabolized and cleared by the kidney. apo A-I, apolipoprotein A-I; HL, hepatic lipase; LPL, lipoprotein lipase; SR-B1, scavenger receptor-B1; VLDL, very low-density lipoprotein.

on nascent HDL. A host of metabolic changes commonly found in obese people can alter apo A-I production. The effects of these variables on the molecular mechanisms of reduced apo A-I in obesity will be discussed.

EFFECT OF OBESITY-RELATED CHANGES ON apo A-I EXPRESSION

The literature on the effect of the metabolic changes commonly associated with obesity on apo A-I production is extensive (Table 2). Obesity is associated with insulin resistance, hyperinsulinemia, carbohydrate intolerance, increased production of adipokines and inflammatory cytokines, changes in prostaglandin metabolism, and neuroendocrine hormonal changes that affect apo A-I production.

Insulin signaling and glucose metabolism are important modulators of apo A-I production. Studies *in vivo* and in hepatocyte cell cultures have shown that glucose suppresses and insulin upregulates the expression of apo A-I protein and its mRNA (38,39). These changes occur at the transcriptional level where the apo A-I promoter activity is suppressed by dextrose and stimulated by insulin in a dose-dependent fashion (38). A 50-base pair fragment spanning nucleotides -425 to -376 within the promoter mediates the effects of both dextrose and insulin. Within this DNA fragment, between -411 and -404, there is an insulin response core element. Mutation of this motif abolishes the effects of both insulin and dextrose. However, it is likely that there are additional carbohydrate-responsive elements within the promoter (38).

The stimulatory effect of insulin on apo A-I promoter is also observed with insulinomimetics such as bisperoxo (1, 10-phenanthroline) oxovanadate (bpv) and the protein kinase C activator phorbol ester phorbol-12, 13-dibutyrate (39). However, insulin sensitization with thiazolidinediones may not always be sufficient to induce apo A-I expression (43,44). Moreover, insulin therapy fails to correct the metabolic abnormalities of apo A-I in people with type 2 diabetes (45). Another argument against a direct role of insulin resistance is the observation that insulin resistance and hyperinsulinemia induced with a high-fructose diet in rats is associated with increased apo A-I levels (46). Similarly, aging in rats is associated with increased expression of apo A-I although it is accompanied with insulin resistance (47). These observations may well be species-specific or may be viewed as suggestive evidence that insulin resistance *per se* is not a direct cause of low apo A-I and HDLc in obesity. It is noteworthy that observational data derived from the Lipid Research Clinics indicate that HDLc rises after the age of 40 years in white men and in white women who are nonsex hormone users (48).

The potential mediators of insulin resistance in obesity include increased plasma free-fatty acid concentrations or increased muscle and hepatic tissue content of triglycerides, increased production of leptin, inflammatory cytokines such as tumor necrosis factor- α , and possibly other yet unidentified humoral mediators (49).

The free-fatty acid may have a direct albeit a modest effect on apo A-I

production. Free-fatty acid treatment of human hepatoma cell line Hep G2 abolishes insulin activation of apo A-I promoter. However, basal apo A-I gene expression is not altered (50).

Another potential mediator of insulin resistance is leptin (49). Plasma leptin levels correlate with body adiposity and hyperleptinemia occurs in diet-induced models of insulin resistance (51,52). However, treatment of HepG2 cells with leptin over a wide concentration range (0–100 ng/ml) does not alter apo A-I promoter activity, apo A-I protein synthesis, or apo A-I mRNA levels (A.D.M. and M.J.H., unpublished data). These observations do not support a role of leptin in contributing to the obesity-related reduction in apo A-I levels.

Inflammatory cytokines are implicated in obesity-related insulin resistance (49). Tumor necrosis factor- α and interleukin-1 β reduce apo A-I gene expression in a dose-dependent manner (40). This effect occurs at the transcriptional level through reduction in apo A-I promoter activity and is mediated through extracellular-signal regulated kinase and *c-jun*-N-terminal kinase signaling and a cytokine responsive element within site A of the promoter (40,41).

Prostanoids are implicated in insulin signaling in the liver and therefore may modulate the apo A-I expression. In addition, some prostanoids are ligands of peroxisome proliferator-activator receptors (53), and peroxisome proliferator-activator receptors are implicated in the regulation of apo A-I expression (54). Decreasing prostaglandin synthesis through cyclooxygenase inhibition with indomethacin downregulates apo A-I protein and mRNA expression at a transcriptional level (55). This effect could not be attributed to either arachidonic acid excess or to a deficiency in various prostanoids tested including prostaglandin I₂, thromboxane B₂, (\pm) 5-HETE or (\pm) 12-HETE, and prostaglandin E₁ and E₂ (55). Thus, the underlying mechanism of indomethacin-related downregulation of apo A-I expression is not known.

Obesity-related reduction in apo A-I is not only related to increased plasma

Table 2 Obesity-related metabolic changes that may alter hepatic apo A-I gene transcription

Metabolic variables	Effect on apo A-I	References
Hyperinsulinemia	Stimulate	38,39
Insulin resistance	Inhibit	38,39
Hyperglycemia	Inhibit	38
Increased FFA	Inhibit insulin-mediated effects	50
	No effect on basal rate of transcription	
Increased TNF- α /IL-1 β	Inhibit	40,41
Hyperleptinemia	No effect	A.D.M. and M.J.H., unpublished data
Endocannabinoids	Inhibit	60

apo A-I, apolipoprotein A-I; FFA, free-fatty acid; IL-1 β , interleukin-1 β ; TNF- α , tumor necrosis factor- α .

clearance of the protein but also is the result of down regulation of apo A-I production. Although the precise nature for this change is not known it is likely that increased cytokine production and possibly impaired insulin signaling or carbohydrate intolerance may contribute significantly to the inhibition of apo A-I gene transcription.

EFFECT OF NUTRIENT INTAKE ON HDLc AND apo A-I

The effect of obesity on HDLc and apo A-I levels is modulated by nutrient consumption. Total caloric intake and consumption of specific nutrients have significant effects on plasma HDLc concentration. Since medical nutrition therapy constitutes the cornerstone of obesity management, it is essential to understand the mechanisms underlying the changes in HDLc level in response to alterations in dietary intake.

EFFECT OF CALORIC INTAKE

Total energy flux has an important role in modulating the plasma levels of HDLc. In addition, weight loss is associated with increased LPL levels and LCAT activity that contribute to the increased cholesterol esterification and RCT (56).

A meta-analysis of 70 studies indicated that reduced caloric intake during a weight reducing program is associated with a temporary decline in HDLc (57). Once a stable weight is achieved, HDLc is increased. It is estimated that for every kilogram decrease in body weight, a 0.35 mg/dl (0.009-mmol/l) increase in HDLc occurs for subjects at a stabilized body weight, while HDLc will decrease by 0.27 mg/dl (0.007-mmol/l)/kg lost in subjects actively losing weight (57).

In some studies where pharmacologic agents were used for weight loss, the rise in HDLc is more favorable than what would be expected from weight loss secondary to caloric restriction alone. In clinical trials with appetite suppressant sibutramine, a loss of 10 lb (4.5 kg) was associated with 20.7% increase in HDLc while total cholesterol was decreased by 16% and LDLc decreased by 12% (58).

Selective CB1-receptor blockade with rimonabant significantly reduces body

weight and improves the lipid profile (59). As compared with placebo, rimonabant at a dose of 20 mg was associated with a mean weight loss of 5.4 kg along with ~10.0% increase in HDLc (59). Although most of the effect on HDLc may well be the result of weight loss and specifically loss of abdominal fat, rimonabant may have direct effects on apo AI production; some laboratory experiments suggest that endocannabinoids may have suppressive effect on apo A-I gene transcription (60).

Orlistat, a gastrointestinal lipase inhibitor that reduces dietary fat absorption by 30%, promotes modest weight loss of ~5% of body weight, reduces the LDLc levels but is not associated with increased plasma levels of HDLc (61,62). The lack of favorable change in HDLc level after orlistat treatment could be secondary to limited weight reduction or more likely related to the altered nutrient absorption notably reduced saturated fatty acid influx. The latter is known to be an important modulator of HDLc levels (16).

Gastric reduction surgery is an effective weight loss treatment for obesity. It is associated with reduction in caloric consumption as well as in changes in neuroendocrine hormones of the gut. The effect of these changes on HDL physiology is not well studied. However, in the Swedish Obese Subjects Study, a 10-year follow-up of individuals undergoing bariatric surgery has found that all cardiovascular risk factors except hypercholesterolemia improved in the surgical patients (63). In these studies, the body weight in the control group increased by 0.1% after 2 years of follow-up while it decreased by 23.4% in the surgery group (63). After 10 years, the weight had increased by 1.6% in controls and decreased by 16.1% in surgery group (63). Recovery from hypertension, diabetes, hypertriglyceridemia, a low HDLc level, and hyperuricemia was more frequent in the surgical group than in the control group, both at 2 and 10 years of follow-up. Hypercholesterolemia did not improve significantly in the surgical group.

Caloric restriction to achieve desirable body weight either with life style changes alone or when coupled with pharmacologic or surgical interventions may have cardio-protective effects (64,65).

EFFECT OF DIETARY COMPOSITION

The response of plasma lipids to dietary changes depends on genetic factors and the individual's lipid phenotype (66). Overall, replacing saturated fat with carbohydrate in the diet is associated with reduced HDLc along with reduced LDLc and increased triglycerides levels (67–71). Conversely, replacement of dietary carbohydrate with fat results in lower triglyceride and higher HDLc concentrations if the body weight is not altered. Thus, a diet rich in glycemic load is associated with reduced HDLc levels (69).

The effect of replacing saturated fat with monounsaturated or polyunsaturated fat on HDLc is less dramatic. In general, reducing dietary intake of saturated fat is associated with reduced plasma cholesterol content of various lipoproteins including HDL (67–70). The reduced cholesterol content of HDL accelerates its clearance.

The mechanisms by which saturated fatty acids and cholesterol raise plasma HDLc do not involve transcriptional regulation of the apo A-I gene (50). Under basal conditions, free-fatty acid treatment of HepG2 cells do not alter apo A-I mRNA or its protein levels but they can abolish insulin and transcription factor Sp-1-stimulated activation of the apo A-I promoter (50). In contrast, unsaturated fatty acids had no effect on Sp1-mediated induction of the apo A-I promoter. The overall contribution of these changes in apo A-I gene transcription to overall changes of HDLc is probably small. In contrast, the changes in HDLc turnover are more important. Thus, polyunsaturated fatty acids upregulate hepatic scavenger receptor class B type 1 expression, increase HDLc ester transport to the liver, and as a consequence, plasma HDLc level is reduced (72). It is noteworthy that diets enriched in saturated fatty acids, unlike diets enriched in unsaturated fatty acids, are associated with increased HDLc and in apo A-II levels but not in apo A-I levels (73). This effect is gender specific. In general, men may have a more favorable lipoprotein response to a low fat, low cholesterol diet than postmenopausal women (74,75). The selective changes in apo AI and AII provide an additional rationale for the current dietary

recommendations of limiting intake of saturated fat in the diet.

The triglyceride-lowering effect of *omega*-3 fat consumption is well established (76). Sometimes, *omega*-3 fatty acid-related decrease in plasma triglyceride level is associated with a modest reduction in HDLc possibly through increasing the fractional catabolic rate of medium-sized HDL particles (76). However, clinical trials with a purified *omega*-3 fatty acid formulation, namely Omacor, have shown either a modest increase or no change in plasma HDLc levels. It is possible that the increased fractional catabolic clearance of HDLc is counterbalanced and sometimes superseded by the reduced CETP-mediated exchange of HDL-cholesterol ester for VLDL-triglycerides (77).

The effect of monounsaturated fatty acids on apo A-I expression in liver is comparable with the effects of polyunsaturated fatty acids (78). *Trans*-fatty acids or hydrogenated fat-enriched diets increase LDLc levels, and either decrease or have no effect on HDLc and apo A-I levels (79–82).

The effect of monosaccharides other than glucose on apo A-I gene expression has not been well studied. Fructose-enriched diets may increase cardiovascular risk factors, especially in hyperinsulinemic men (83). However, consumption of fructose as high as 60 g/day incorporated in the normal diets of 13 type 2 diabetic patients did not significantly alter fasting serum lipids and apo A-I and B-100 levels (84).

The effect of dietary protein on HDLc is not well studied (85,86). Some proteins such as soy protein have a unique, albeit, modest direct effects on HDLc (87,88). Often it is not possible to determine the effects of protein independently of the effects of changing the proportions of fat and carbohydrates in the diet (85). Replacing carbohydrates with protein in the Optimal Macro-Nutrient Intake Heart Trial to Prevent Heart Disease (OMNI-Heart) have shown modest improvements in blood pressure and HDLc levels (89). This is probably the result of limiting the glycemic load rather than a consequence of increasing the protein load (69).

Commonly used nutritional supplements also affect HDLc metabolism.

Large doses of antioxidant vitamins may partially blunt HDLc induction by simvastatin and niacin combination therapy (90). The apo A-I promoter is sensitive to the oxidative state of the cell and some antioxidants, at high concentrations, can suppress apo A-I promoter activity (91). Apo A-I gene transcription is also affected by large doses of vitamin D (92) and vitamin A (93). Optimal concentration of these vitamins are needed for apo A-I gene expression. The relationship between vitamin D, HDLc, and obesity has been the subject of several epidemiologic studies. Parikh *et al.* in a cohort of 300 otherwise healthy individuals showed an inverse relationship between body mass index as well as fat mass when compared with serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (94). The same inverse relationship of adiposity and 25-hydroxyvitamin D was found in a follow-up study (95). Using data derived from NHANES III, Ford *et al.* found that as serum 25-hydroxyvitamin D levels rose, the prevalence of low HDLc declined (96). A similar observation was made in untreated subjects with polycystic ovary syndrome, a disease associated with insulin resistance. In the latter study, 25-hydroxyvitamin D levels were directly correlated with serum HDLc (97).

Alcoholic beverages have significant effects on HDLc. Moderate alcohol consumption (1–2 drinks/day) may decrease cardiovascular disease risk. This favorable effect may be partly related to improved plasma lipid profile with increased concentrations of HDLc (98,99). In addition, treatment of hepatoma cells in culture with alcohol significantly increases apo A-I production while decreasing apo B production (100).

EFFECT OF EXERCISE

Most programs targeting body weight reduction include an exercise component. Exercise increases HDLc levels especially in people with high baseline HDLc (>60 mg/dl) (101). In general, a relatively high intensity exercise is required for significant changes in plasma HDLc concentrations. The magnitude of the change in HDLc may depend on genetic factors notably the genotypes of CETP and endothelial lipase (102,103).

Although the effect of exercise is generally modest, it should be encouraged because it helps maintain weight loss and can also improve insulin sensitivity independent of weight loss.

CONCLUSIONS

The low plasma HDLc concentrations in obese people could be the result of a number of metabolic changes. For simplification purposes these changes can be categorized into two general groups; (i) increased fractional clearance of HDL secondary to reduced cholesterol content, and (ii) reduced production of the main cardioprotective apoprotein, notably apo A-I. Although low HDLc levels in obese people are commonly a concomitant of hypertriglyceridemia, it can occur independently of elevated serum triglyceride levels. In some obese subjects, the low HDLc concentration may be secondary to elevated serum levels of inflammatory cytokines.

Recent observations with agents that interfere with cholesterol ester transfer suggest that the mechanistic determinant of HDLc levels is an important predictor of its cardioprotective properties. To this end, caloric intake and select nutrients play an important role in modulating both the fractional clearance rate as well as the rate of apo A-I gene expression. Understanding the mechanisms of low HDL in obesity will help in the development of interventions that reduce the risk of cardiovascular disease in people with excess adiposity.

DISCLOSURE

The authors declared no conflict of interest.

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REFERENCES

1. Willett WC, Manson JE, Stampfer MJ *et al.* Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA* 1995;273:461–465.
2. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North Am men after a 26 year observation period: the Manitoba Study. *Am J Cardiol* 1977;39:452–458.
3. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67:968–977.
4. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity

- as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002;162:1867–1872.
5. Manson JE, Colditz GA, Stampfer MJ *et al*. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 1990;322:882–889.
 6. Dagenais GR, Yi Q, Mann JF *et al*. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J* 2005;149:54–60.
 7. Poirier P, Giles TD, Bray GA *et al*. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113:898–918.
 8. Isomaa B, Almgren P, Tuomi T *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
 9. Lakka HM, Laaksonen DE, Lakka TA *et al*. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709–2716.
 10. López-Candales A. Metabolic syndrome X: a comprehensive review of the pathophysiology and recommended therapy. *J Med* 2001;32:283–300.
 11. Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol* 1991;67:1185–1189.
 12. Haffner SM, American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004;27(Suppl 1):S68–S71.
 13. Hopkins PN, Heiss G, Ellison RC *et al*. Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. *Circulation* 2003;108:519–523.
 14. Semenkovich CF. Insulin resistance and atherosclerosis. *J Clin Invest* 2006;116:1813–1822.
 15. Szapary PO, Rader DJ. The triglyceride-high-density lipoprotein axis: an important target of therapy? *Am Heart J* 2004;148:211–221.
 16. Mooradian AD, Haas MJ, Wong NCW. The effect of select nutrients on serum high density lipoprotein cholesterol and apolipoprotein A-I levels. *Endocr Rev* 2006;27:2–16.
 17. Mooradian AD, Haas MJ, Wong NCW. Transcriptional control of apolipoprotein A-I gene expression in diabetes mellitus. *Diabetes* 2004;53:513–520.
 18. Hachem S, Mooradian AD. Familial dyslipidemias: an overview of pathophysiology and management. *Drugs* 2006;66:1949–1969.
 19. Nissen SE, Tardif J-C, Nicholls SJ *et al*. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;356:1304–1316.
 20. Borggreve SE, Hillege HL, Wolfenbittel BH *et al*. An increased coronary risk is paradoxically associated with common cholesteryl ester transfer protein gene variations that relate to higher high-density lipoprotein cholesterol: a population-based study. *J Clin Endocrinol Metab* 2006;91:3382–3388.
 21. Vaisar T, Pennathur S, Green PS *et al*. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *J Clin Invest* 2007;117:746–756.
 22. Kawahiri M, Maugeais C, Rader D. High-density lipoprotein metabolism: molecular targets for new therapies for atherosclerosis. *Curr Atheroscler Rep* 2000;2:363–372.
 23. Wang M, Briggs MR. HDL: the metabolism, function, and therapeutic importance. *Chem Rev* 2004;104:119–137.
 24. Zheng L, Nukuna B, Brennan ML *et al*. Apolipoprotein A-I is a selective target for myeloperoxidase-catalyzed oxidation and functional impairment in subjects with cardiovascular disease. *J Clin Invest* 2004;114:529–541.
 25. Navab M, Anantharamaiah GM, Reddy ST *et al*. Mechanisms of disease: proatherogenic HDL—an evolving field. *Nat Clin Pract Endocrinol Metab* 2006;2:504–511.
 26. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
 27. Park YW, Zhu S, Palaniappan L *et al*. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2003;163:427–436.
 28. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003;52:1210–1214.
 29. Meigs JB, Wilson PW, Nathan DM *et al*. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 2003;52:2160–2167.
 30. Smith SC. Multiple risk factors for cardiovascular disease and diabetes mellitus. *Am J Med* 2007;120(3 Suppl 1):S3–S11.
 31. Brown CD, Higgins M, Donato KA *et al*. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 2000;8:605–619.
 32. Mooradian AD, Albert SG, Hass MJ. Low serum HDL cholesterol in obese subjects with normal serum triglycerides: the role of insulin resistance and inflammatory cytokines. *Diabetes Obes Metab* 2007;9:441–443.
 33. Borggreve SE, De Vries R, Dullaart RP. Alterations in high-density lipoprotein metabolism and reverse cholesterol transport in insulin resistance and type 2 diabetes mellitus: role of lipolytic enzymes, lecithin: cholesterol acyltransferase and lipid transfer proteins. *Eur J Clin Invest* 2003;33:1051–1069.
 34. Vajo Z, Terry JG, Brinton EA. Increased intra-abdominal fat may lower HDL levels by increasing the fractional catabolic rate of Lp A-I in postmenopausal women. *Atherosclerosis* 2002;160:495–501.
 35. de Vries R, Kerstens MN, Sluiter WJ *et al*. Cellular cholesterol efflux to plasma from moderately hypercholesterolaemic type 1 diabetic patients is enhanced, and is unaffected by simvastatin treatment. *Diabetologia* 2005;48:1105–1113.
 36. de Vries R, Groen AK, Perton FG *et al*. Increased cholesterol efflux from cultured fibroblasts to plasma from transfer hypertriglyceridemic type 2 diabetic patients: roles of pre beta-HDL, phospholipid protein and cholesterol esterification. *Atherosclerosis* 2008;196:733–741.
 37. Dullaart RP, De Vries R, Scheek L *et al*. Type 2 diabetes mellitus is associated with differential effects on plasma cholesteryl ester transfer protein and phospholipid transfer protein activities and concentrations. *Scand J Clin Lab Invest* 2004;64:205–215.
 38. Murao K, Wada Y, Nakamura T *et al*. Effects of glucose and insulin on rat apolipoprotein A-I gene expression. *J Biol Chem* 1998;273:18959–18965.
 39. Lam JK, Matsubara S, Mihara K *et al*. Insulin induction of apolipoprotein A, role of Sp1. *Biochemistry* 2003;42:2680–2690.
 40. Haas MJ, Horani M, Mreyoud A *et al*. Suppression of apolipoprotein AI gene expression in HepG2 cells by TNF alpha and IL-1beta. *Biochem Biophys Acta* 2003;1623:120–128.
 41. Beers A, Haas MJ, Wong NCW, Mooradian AD. Inhibition of apolipoprotein AI gene expression by tumor necrosis factor alpha: roles for MEK/ERK and JNK signaling. *Biochemistry* 2006;45:2408–2413.
 42. Le NA, Ginsburg HN. Heterogeneity of apolipoprotein A-I turnover in subjects with reduced concentrations of plasma high density lipoprotein cholesterol. *Metabolism* 1988;37:614–617.
 43. Mooradian AD, Haas MJ, Wong NCW, Chehade JH. Apolipoprotein A-I expression in rats is not altered by troglitazone. *Exp Biol Med (Maywood)* 2002;227:1001–1005.
 44. Sakamoto J, Kimura H, Moriyama S *et al*. Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun* 2000;278:704–711.
 45. Duvillard L, Pont F, Florentin E, Gambert P, Vergès B. Inefficiency of insulin therapy to correct apolipoprotein A-I metabolic abnormalities in non-insulin-dependent diabetes mellitus. *Atherosclerosis* 2000;152:229–237.
 46. Mooradian AD, Wong NCW, Shah GN. Apolipoprotein A1 expression in young and aged rats is modulated by dietary carbohydrates. *Metabolism* 1997;46:1132–1136.
 47. Shah NG, Wong NCW, Mooradian AD. Age-related changes in apolipoprotein A-I expression. *Biochem Biophys Acta* 1995;1259:277–282.
 48. Population Studies Data Book Volume 1. The Lipid Research Clinics. NIH publication No. 80-1527, July 1980.
 49. Mooradian AD. Obesity: a rational target for managing diabetes mellitus. *Growth Horm IGF Res* 2001;11(Suppl A):S79–S83.
 50. Haas MJ, Horani MH, Wong NCW, Mooradian AD. Induction of the apolipoprotein AI promoter by Sp1 is repressed by saturated fatty acids. *Metabolism* 2004;53:1342–1348.
 51. Mooradian AD, Chehade J, Hurd R, Haas MJ. Monosaccharide-enriched diets cause hyperleptinemia without hypophagia. *Nutrition* 2000;16:439–441.
 52. Mooradian AD, Chehade J. Serum leptin response to endogenous hyperinsulinemia in aging rats. *Mech Ageing Dev* 2000;115:101–106.

53. Dussault I, Forman BM. Prostaglandins and fatty acids regulate transcriptional signaling via the peroxisome proliferator activated receptor nuclear receptors. *Prostaglandins other Lipid Mediat* 2000;62:1–13.
54. Vu-Dac N, Chopin-Delannoy S, Gervois P *et al.* The nuclear receptors peroxisome proliferator-activated receptor α and Rev-erb α mediate the species-specific regulation of apolipoprotein A₁ expression by fibrates. *J Biol Chem* 1998;273:25713–25720.
55. Horani M, Gopal F, Haas MJ, Wong NCW, Mooradian AD. Cyclooxygenase (COX) inhibition is associated with downregulation of apolipoprotein AI promoter activity in cultured hepatoma cell line-HepG2. *Metabolism* 2004;53:174–181.
56. Weisweiler P. Plasma lipoproteins and lipase and lecithin: cholesterol acyltransferase activities in obese subjects before and after weight reduction. *J Clin Endocrinol Metab* 1987;65:969–973.
57. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;56:320–328.
58. James WP, Astrup A, Finer N *et al.* Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;356:2119–2125.
59. Després JP, Goy A, Sjöström L, Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005;353:2121–2134.
60. Ligaray K, Hachem S, Mazza A *et al.* Repression of apolipoprotein A-I gene expression by anandamide. *Diabetes* 2007;56(Suppl 1):A56.
61. Davidson MH, Hauptman J, DiGirolamo M *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;281:235–242.
62. Sjöström L, Rissanen A, Andersen T *et al.* Randomized placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;352:167–172.
63. Sjöström L, Lindroos AK, Peltonen M *et al.* Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;35:2683–2693.
64. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ *et al.* Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82–96.
65. Bantle JP, Wylie-Rosett J, Albright AL *et al.* Nutrition recommendations and interventions for diabetes—2006: a position statement of the American Diabetes Association. *Diabetes Care* 2006;29:2140–2157.
66. Krauss RM. Dietary and genetic probes of atherogenic dyslipidemia. *Arterioscler Thromb Vasc Biol* 2005;25:2265–2272.
67. Berglund L, Oliver EH, Fontanez N *et al.* HDL-subpopulation patterns in response to reductions in dietary total and saturated fat intakes in healthy subjects. *Am J Clin Nutr* 1999;70:992–1000.
68. Pelkman CL, Fishell VK, Maddox DH *et al.* Effects of moderate-fat (from monounsaturated fat) and low-fat weight-loss diets on the serum lipid profile in overweight and obese men and women. *Am J Clin Nutr* 2004;79:204–212.
69. Slyper A, Jurva J, Pleuss J, Hoffmann R, Gutterman D. Influence of glycemic load on HDL cholesterol in youth. *Am J Clin Nutr* 2005;81:376–379.
70. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146–1155.
71. Meksawan K, Pendergast DR, Leddy JJ *et al.* Effect of low and high fat diets on nutrient intakes and selected cardiovascular risk factors in sedentary men and women. *J Am Coll Nutr* 2004;23:131–140.
72. Hatahet W, Cole L, Kudchodkar BJ, Fungwe TV. Dietary fats differentially modulate the expression of lecithin: cholesterol acyltransferase, apoprotein-A1 and scavenger receptor b1 in rats. *J Nutr* 2003;133:689–694.
73. Sánchez-Muniz FJ, Merinero MC, Rodríguez-Gil S *et al.* Dietary fat saturation affects apolipoprotein AI levels and HDL composition in postmenopausal women. *J Nutr* 2002;132:50–54.
74. Walden CE, Retzlaff BM, Buck BL *et al.* Differential effect of National Cholesterol Education Program (NCEP) Step II diet on HDL cholesterol, its subfractions, and apoprotein A-I levels in hypercholesterolemic women and men after 1 year: the beFIT Study. *Arterioscler Thromb Vasc Biol* 2000;20:1580–1587.
75. Li Z, Otvos JD, Lamon-Fava S *et al.* Men and women differ in lipoprotein response to dietary saturated fat and cholesterol restriction. *J Nutr* 2003;133:3428–3433.
76. Harris WS. n-3 Fatty acids and lipoproteins: comparison of results from human and animal studies. *Lipids* 1996;31:243–252.
77. Bays H. Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. *Am J Cardiol* 2006;98:711–76i.
78. Brousseau ME, Ordovas JM, Osada J *et al.* Dietary monounsaturated and polyunsaturated fatty acids are comparable in their effects on hepatic apolipoprotein mRNA abundance and liver lipid concentrations when substituted for saturated fatty acids in cynomolgus monkeys. *J Nutr* 1995;125:425–436.
79. Judd JT, Baer DJ, Clevidence BA *et al.* Dietary cis and trans monounsaturated and saturated FA and plasma lipids and lipoproteins in men. *Lipids* 2002;37:123–131.
80. Methane NR, Welty FK, Barrett PH *et al.* Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women. *Arterioscler Thromb Vasc Biol* 2004;24:1092–1097.
81. Zock PL, Katan MB. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 1992;33:399–410.
82. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* 1990;323:439–445.
83. Reiser S, Powell AS, Scholfield DJ *et al.* Blood lipids, lipoproteins, apoproteins, and uric acid in men fed diets containing fructose or high-amylose cornstarch. *Am J Clin Nutr* 1989;49:832–839.
84. Osei K, Bossetti B. Dietary fructose as a natural sweetener in poorly controlled type 2 diabetes: a 12-month crossover study of effects on glucose, lipoprotein and apolipoprotein metabolism. *Diabet Med* 1989;6:506–511.
85. Lichtenstein AH. Thematic review series: patient-oriented research. Dietary fat, carbohydrate, and protein: effects on plasma lipoprotein patterns. *J Lipid Res* 2006;47:1661–1667.
86. Vega-López S, Lichtenstein AH. Dietary protein type and cardiovascular disease risk factors. *Prev Cardiol* 2005;8:31–40.
87. Potter SM. Overview of proposed mechanism for the hypocholesterolemic effect of soy. *J Nutr* 1995;125(Suppl 3):S606–S611.
88. Lamon-Fava S, Micherone D. Regulation of apoA-I gene expression: mechanism of action of estrogen and genistein. *J Lipid Res* 2004;45:106–112.
89. Appel LJ, Sacks FM, Carey VJ *et al.* Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005;294:2455–2464.
90. Cheung MC, Zhao X-Q, Chait A, Albers JJ, Brown G. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler Thromb Vasc Biol* 2001;21:1320–1326.
91. Mooradian AD, Haas MJ, Wadud K. Ascorbic acid and alpha-tocopherol down-regulate apolipoprotein A-I gene expression in HepG2 and Caco-2 cell lines. *Metabolism* 2006;55:159–167.
92. Wehmeier K, Beers A, Haas MJ *et al.* Inhibition of apolipoprotein AI gene expression by 1, 25-dihydroxyvitamin D₃. *Biochim Biophys Acta* 2005;1737:16–26.
93. Berthou L, Langouet S, Grude P *et al.* Negative regulation of Apo A-I gene expression by retinoic acid in rat hepatocytes maintained in a coculture system. *Biochim Biophys Acta* 1998;1391:329–336.
94. Parikh SJ, Edelman M, Uwaifo GI *et al.* The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004;89:1196–1199.
95. Snijder MB, van Dam RM, Visser M *et al.* Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005;90:4119–4123.
96. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care* 2005;28:1228–1230.
97. Hahn S, Haselhorst U, Tan S *et al.* Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes* 2006;114:577–583.

98. Baer DJ, Judd JT, Clevidence BA *et al*. Moderate alcohol consumption lowers risk factors for cardiovascular disease in postmenopausal women fed a controlled diet. *Am J Clin Nutr* 2002;75:593–599.
99. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and low risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523–1528.
100. Tam SP. Effect of ethanol on lipoprotein secretion in two human hepatoma cell lines, HepG2 and Hep3B. *Alcohol Clin Exp Res* 1992;16:1021–1028.
101. Williams PT. The relationships of vigorous exercise, alcohol, and adiposity to low and high high-density lipoprotein-cholesterol levels. *Metabolism* 2004;53:700–709.
102. Wilund KR, Ferrell RE, Phares DA, Goldberg AP, Hagberg JM. Changes in high-density lipoprotein-cholesterol subfractions with exercise training may be dependent on cholesteryl ester transfer protein (CETP) genotype. *Metabolism* 2002;51:774–778.
103. Halverstadt A, Phares DA, Ferrell RE *et al*. High-density lipoprotein-cholesterol, its subfractions, and responses to exercise training are dependent on endothelial lipase genotype. *Metabolism* 2003;52:1505–1511.