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review

Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet

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Abstract **Hepatic lipase (HL) plays a central role in LDL and HDL remodeling. High HL activity is associated with small, dense LDL particles and with reduced HDL_2 cholesterol levels. HL activity is determined by an HL gene promoter polymorphism, by gender (lower in premenopausal women), and by visceral obesity with insulin resistance. The activity is affected by dietary fat intake and selected medications. There is evidence for an interaction of the HL promoter polymorphism with visceral obesity, dietary fat intake, and with lipid-lowering medications in determining the level of HL activity. The dyslipidemia with high HL activity is a potentially proatherogenic lipoprotein profile in the metabolic syndrome, in Type 2 diabetes, and in familial combined hyperlipidemia.**—Deeb, S. S., A. Zambon, M. C. Carr, A. F. Ayyobi, and J. D. Brunzell. **Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet.** ***J. Lipid Res.*** **2003.** 44: **1279–1286.**

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Hepatic lipase (HL) is a key enzyme involved in lipoprotein metabolism. Its catalytic activity contributes to the remodelling of chylomicron remnants, IDLs, LDLs, and HDLs, and participates in the reverse cholesterol transport (1). These effects possibly influence the process of atherosclerosis. Recent reviews on HL have focused on its evolution (2), structure, function, and regulation (3), and its potential role in atherosclerosis (4). The focus of this review will be on the interaction between genetic variants, obesity, sex hormones, and diet in influencing HL activity and on clinical implications of variation in this activity.

HL AND DYSLIPIDEMIA

Lipolytic role of HL in remodeling of human remnant and LDL

In vitro and in vivo studies have clearly demonstrated that HL plays a key role in lipoprotein metabolism (5, 6). Multiple lines of evidence suggest that human HL modulates the lipid composition of IDL remnants and large, buoyant LDLs, resulting in denser lipoprotein particles both in patients with cardiovascular disease (CVD) and in normal subjects (7, 8). LDL size and buoyancy are inversely proportional to HL activity, which seems to be correlated also with both the fractional catabolic rate and the input rate of LDL apolipoprotein B (apoB) in men with varying plasma triglyceride (TG) concentrations (9). Patients with high HL have smaller, denser LDL particles, relatively depleted in phospholipids (PLs) and free cholesterol, as compared with subjects with low HL activity (7) (**Fig. 1A**). Individuals with CVD, characterized by the predominance of small, dense LDL as determined by gradient gel electrophoresis (also defined as pattern B LDL subclass distribution), have significantly higher HL activity than patients with CVD but large, buoyant LDL particles (pattern A) (10). Interestingly, HL activity is not associated with LDL cholesterol levels.

More direct evidence that HL plays a key role in human lipoprotein metabolism is obtained from studies of individuals with HL deficiency. Few patients with true HL deficiency have been identified (1, 11). Patients with complete HL deficiency present with elevated plasma concentrations of cholesterol and TG, and with a lipoprotein profile characterized by the presence of large β-VLDL and large, buoyant TG- and PL-enriched LDL and HDL particles (12, 13). These large LDL particles contain apoB-100 as their main apolipoprotein and very little, if any, apoE, truly representing a "metabolic end-product" of the apoB-containing lipoprotein cascade in these HL-deficient patients. Moreover, incubation of these large, buoyant LDL particles from an HL-deficient subject with active human HL resulted in the formation of LDL of "normal" density and lipid composition (12). This enzyme appears to be rate limiting for the hydrolysis of TG in these lipoproteins.

Lipolytic role of HL in remodeling of human HDLs

In addition to its acylglycerol hydrolase activity, HL acts as a phospholipase. Studies on isolated HDL particles (14)

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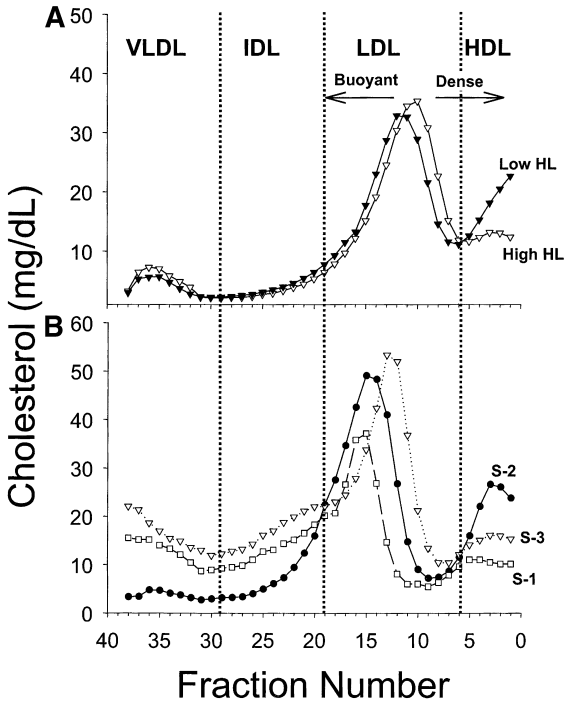

Fig. 1. A: Lipoprotein cholesterol distribution by nonequilibrium density gradient ultracentrifugation in normolipidemic men divided into top and bottom tertiles according to their hepatic lipase (HL) activity (7). Low HL, solid triangles; high HL, open triangles. B: Lipoprotein cholesterol distribution by nonequilibrium density gradient ultracentrifugation in patients with HL deficiency. Subject S-1, open squares; S-2, solid circles; S-3, open triangles. Lipoprotein elution ranges were defined as previously reported (13).

have established that HL hydrolyzes both HDL PLs and TGs. Because of the relatively small molar proportion of TGs in HDL, however, HL hydrolyzes PLs in HDL more extensively than it does TGs. The phospholipase activity may play an important role in the ability of HL to convert the PL-rich, buoyant HDL_2 to smaller HDL_3 particles. Therefore, one would expect an inverse relationship between HL activity and plasma HDL_2 cholesterol concentrations, as indeed was observed in several studies (15–17). Estrogen administration, which decreases HL activity (18), has been shown to increase HDL (19), and in postmenopausal women, to increase HDL_2 and decrease HDL_3 (20). In addition, a common polymorphism (−514 C→T) in the HL gene (*LIPC*) promoter has been observed to associate with lower HL activity and higher concentrations of large HDL_2 particles (21, 22). These results strongly suggest that HL plays an important role in converting large, buoyant HDL to smaller HDL particles with potential implications for reverse cholesterol transport.

It is widely accepted that there is a reversible conversion of HDL_2 to HDL_3; however, as we better understand the influence of various factors on HDL metabolism, a more circular, but unidirectional pathway emerges (**Fig. 2**). This pathway is based on a model in which HDL is formed through an anabolic pathway involving ATP binding cassette A1 and phospholipid transfer protein, starting with apoA-I and its maturation to large apoA-I-only particles. The mature HDL_2 is then directed down the catabolic pathway, where the HDL lipids are removed and particles get progressively smaller until the apoA-I is either cleared through the kidneys or returns into the anabolic pathway (Fig. 2). This anabolic-formative pathway allows for the absorption and transfer of unesterified cholesterol from the periphery to the plasma compartment in anticipation of removal by the liver through the catabolic-degradative pathway in the process of reverse cholesterol transport (23).

Cholesteryl ester (CE)-loaded HDL_2 particles have the potential to deliver CE to the liver. The addition of apoA-II to this particle may direct HDL_2 toward the degradative pathway. There are a few lines of evidence supporting this proposed trigger effect of the apoA-II addition to the HDL particles. First, apoA-I/A-II particles are the preferred substrates for human HL (24). Second, maturation of apoA-I-only HDL (Fig. 2) takes place by the stepwise addition of an apoA-I protein to the particle to form discrete subspecies (25). In contrast, the continuous distribution of apoA-I/A-II HDL particles may be considered characteristic of a degradative process compatible with progressive removal of lipids such that all the intermediate sizes are represented (**Fig. 3**). Third, it has been shown that overexpression of human apoA-II in mice increased the fractional catabolic rate of HDL that contributed to HDL deficiency (26).

Subsequent to the addition of apoA-II, HDL_2 interacts with HL and perhaps CE transfer protein (CETP). HL prefers apoA-I/A-II HDL particles as substrate in humans (24). Hydrolysis of PL and TG in large HDL leads to formation of smaller HDL_3. As this process occurs, CEs may also be transferred into the liver from the HDL particles. This may result from the catalytic or noncatalytic effects of the enzyme (27). CETP transfers CE from CE-rich HDL and exchanges this CE for TG in VLDL and, to a lesser extent, in LDL. This acquired TG is then hydrolyzed by HL; the complementary effects of CETP and HL lead to smaller, denser HDL particles. The CEs transferred to the LDLs are eventually cleared via uptake through the liver. Scavenger receptor class B type 1 (SR-B1) on the surface of hepatocytes can act as a receptor for HDL particles for uptake of HDL-CE (27). HL appears to modulate SR-B1-mediated selective uptake of HDL-CE, as recently demonstrated in vitro (28). It is also conceivable that binding to HL and SR-B1 may occur in concert, such that both activities occur either simultaneously or sequentially.

Role of HL in lipoprotein metabolism independent of its lipolytic function

Recent in vitro data suggest that HL participates with cell surface heparan sulfate proteoglycans and the LDL receptor-like protein (LRP) in promoting uptake of apoB-containing remnant lipoproteins and HDL [reviewed in ref. (6)]. The enhancement of hepatic uptake of apoB-containing lipoproteins was independent of lipolytic activity and did not require apoE (29–31). Several groups have demonstrated direct binding of HL to LRP (29–31). In order to test whether these effects occur in vivo, transgenic mice that overexpressed catalytically active human HL in the liver were generated (32). Both

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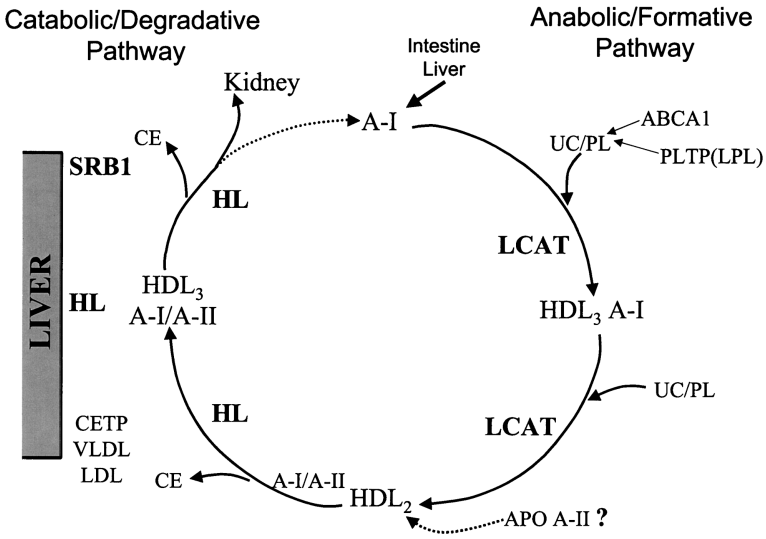

Fig. 2. Circular pathway of HDL formation and degradation. ABCA1, ATP-binding cassette transporter A1; CETP, cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase; LPL, lipoprotein lipase; PL, phospholipid; PLTP, phospholipid transfer protein; SR-BI, scavenger receptor BI; UC, unesterified cholesterol (see text).

apoB-containing remnant lipoproteins and HDL were reduced in these transgenic mice when fed a high-fat diet or after crossing them with mice that overexpress apoB, or with apoE-deficient mice. While the apoB-containing lipoproteins were reduced in mice that overexpressed catalytically inactive HL, HDL was minimally reduced. Other in vitro data strongly suggest a role of HL in SR-BI-mediated HDL-CE selective uptake, which seems to be dependent upon both HL lipolytic function and role as a ligand (28).

Recent evidence in humans supports the concept that HL indeed plays an important role in lipoprotein metabolism independent of its enzymatic activity (13). This study evaluated three patients with complete HL deficiency. All three patients had buoyant LDL compared with normal individuals (Fig. 1B). Two of the patients (S-1 and S-3) were characterized by having neither plasma HL activity nor detectable HL protein; the third subject (S-2) had no plasma HL activity but a detectable amount (35.5 ng/ml) of HL protein (Fig. 1B). Despite expressing a relatively small amount of inactive protein (20% of the HL protein found in normal subjects), Patient S-2 had less cholesterol in the VLDL and IDL elution range as compared with Patients S-1 and S-3, who had neither HL activity nor protein. Furthermore, VLDL and IDL apoB concentrations, reflecting the number of circulating VLDL and IDL particles, were several-fold higher in patients with no protein. These data suggest that even small amounts of inactive HL protein may significantly affect human VLDL and IDL catabolism, as previously observed in vitro and in animal models. Patient S-2 had higher HDL than Patients S-1 and S-3. This finding differs from previous observations in animal models where expression of inactive HL had only minimal effect on HDL levels (32) or was associated with a decrease only in the apoA-II containing subclass of HDL (33). All HL-deficient subjects showed a several-fold increase in lipoprotein TG content across the lipoprotein density spectrum (VLDL, IDL, LDL, and HDL) as compared with controls. Therefore, inactive HL protein appears to affect VLDL and IDL particle concentrations, while HL enzymatic activity seems to influence VLDL, IDL, LDL, and HDL triglyceride content and their physical properties (13).

DETERMINANTS OF HL ACTIVITY

Postheparin plasma HL activity varies widely (about 8-fold) in the general population. The activity is about twice

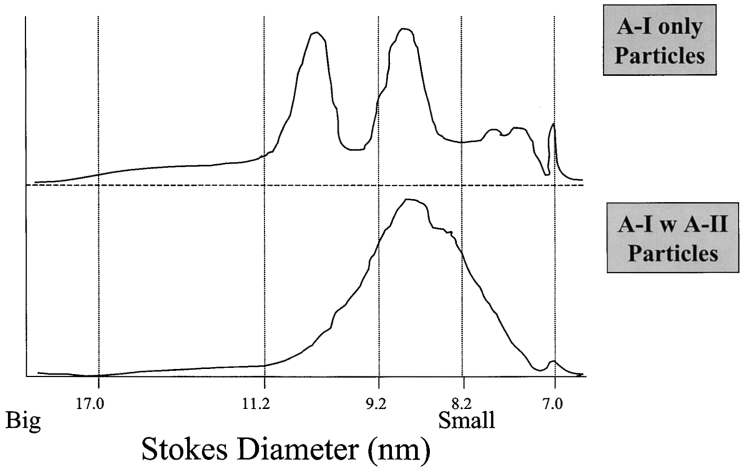

Fig. 3. HDL particle size distribution by gradient gel electrophoresis and densitometric scanning in two subpopulations: HDL particles containing apoA-I only, and HDL particles containing apoA-I and apoA-II (25).

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as high in men as in women, and it differs among ethnic groups. It is estimated that 40–60% of this variability is genetically determined (34). A number of factors are known to either independently or in concert influence HL activity.

Genetic polymorphisms in the promoter of LIPC are associated with HL activity

Four polymorphisms (−250 G to A, −514 C to T, −710 T to C, and −763 A to G) in the promoter of human *LIPC* that are in almost complete linkage disequilibrium were found to be associated with HL activity (21, 35–37). The frequency of the less-common haplotype (with T at position −514) was found to range between 0.15 to 0.21 among Caucasians (21, 35–37), 0.45 to 0.53 among African Americans (21, 38), and 0.47 among Japanese Americans (21). The −514T allele is associated with a 30–40% decrease in HL activity in both men and women (**Fig. 4**), and with a favorable lipoprotein profile characterized by large, buoyant LDL particles (21) and increased HDL_2 cholesterol levels (but not necessarily total HDL cholesterol) (21, 39). In support of the in vivo findings, in vitro analysis indicates that the −C514T substitution reduces transcriptional activity of the *LIPC* promoter (40, 41). The variation in allele frequency between ethnic groups may partially account for the lower HL activity (38), larger, more buoyant LDL particles (42), and higher HDL levels found in Americans of African, Japanese, and Hispanic descent, who have a T allele frequency as high as 0.45–0.50.

Intra-abdominal fat increases HL activity: interaction with the LIPC promoter polymorphism

HL activity is affected by the presence of visceral adiposity (43). As the amount of visceral adiposity increases, HL activity increases until an apparent maximum is reached in both sexes (44). These data demonstrate that a curvilinear relationship fits the association between intra-abdominal fat (IAF) and HL activity. When the maximal level of HL activity is reached by increasing the IAF, HL activity is 33% higher in men than in women with the same *LIPC* promoter genotype. Visceral adiposity and the *LIPC* promoter −514 C to T polymorphism are both associated with variations in HL activity. Recent studies showed that the relationship between central obesity and HL activity is modulated by the *LIPC* promoter polymorphism, such that the presence of the T allele seems to attenuate the increase in HL activity with high levels of IAF (Fig. 4). These results are compatible with lower HL seen in normal men and in men with CAD who carry the T allele (21). The presence of the T allele in patients with visceral obesity, by attenuating the increase in HL activity, may also reduce the atherogenic changes in lipoproteins (↑, small, dense LDL; ↓, HDL_2 cholesterol) associated with visceral obesity. These data suggest a potential role for the HL gene promoter polymorphism in modulating the expression of atherogenic risk factors in the presence of central obesity. Weight loss and a reduction of IAF through caloric restriction are associated with a decrease in HL activity and an increase in LDL particle size (45). This study provided evidence that the reduction in HL activity with decreasing IAF is an important contributor to the increase in LDL size and HDL_2 cholesterol, particularly in those subjects who have small, dense LDL before weight loss.

Ethnic differences in body composition and IAF distribution have been reported. At any level of total body fat, compared with African American subjects, Caucasian sub-

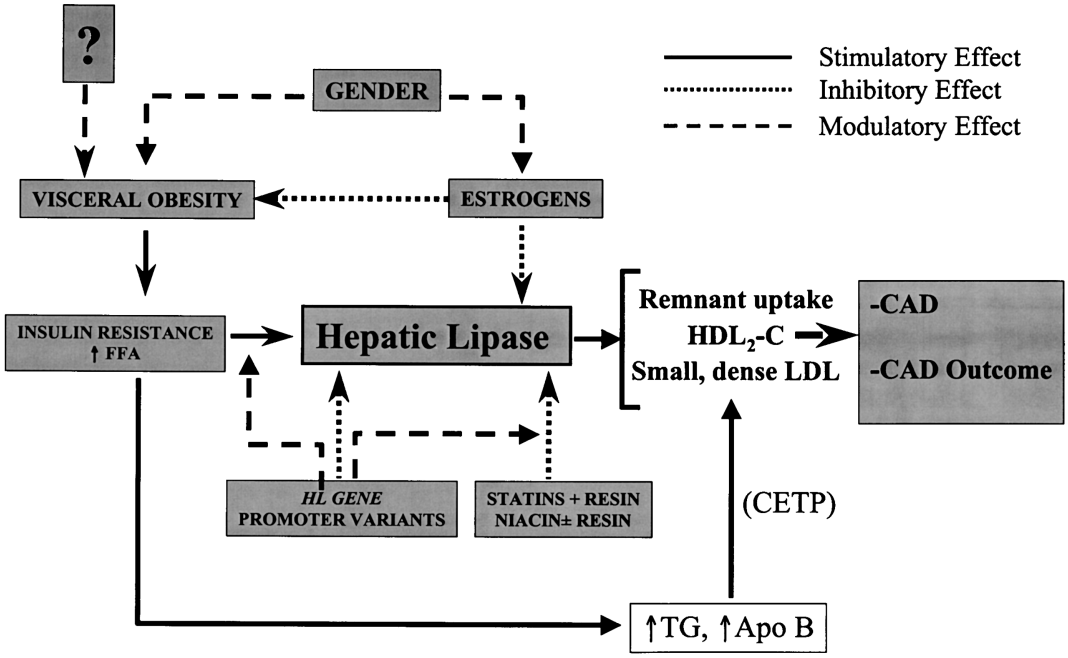

Fig. 4. Determinants of HL activity. The interaction between the *LIPC* promoter polymorphism, gender, intra-abdominal fat, and lipid-lowering medication in determining the level of HL activity, which in turn plays a role in modulating size and density of LDL and HDL, and TG-rich lipoprotein remnant uptake.

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jects have more visceral adipose tissue accumulation (46). Not surprisingly, in both sexes, African Americans showed a significantly reduced HL activity (38). Such a difference in HL activity is of importance because it may contribute to the more favorable plasma lipoprotein profile (buoyant LDL particles and high HDL) of African American individuals compared with Caucasian individuals.

Effects of gender and sex-steroid hormones on HL activity

Men have approximately twice as high HL activity as women (46–50), and gender alone has been shown to account for 28% of the variability in HL activity (49). The gender difference in HL activity has led some to hypothesize that HL activity is a major determinant of the more atherogenic lipoprotein profile in men compared with women (51, 52). Premenopausal women have a less atherogenic lipid profile than men due to higher HDL (53), higher levels of large, buoyant HDL_2 particles (18), and lower triglyceride levels (54). LDL levels in premenopausal women are not consistently lower than in age-matched men (54), but women are less likely than men to have small, dense LDL particles (55) that are more atherogenic than large, buoyant LDL particles (56). The physiological processes that explain the gender dimorphism in HL activity are not well understood but are thought to be a combination of gender differences in sex steroid hormones (57) and body fat distribution (increased visceral adiposity in men).

HL activity has been shown to be highly sensitive to fluctuations in endogenous sex steroids, suggesting a regulatory role. Estrogenic steroids suppress HL activity, while androgenic steroids increase HL activity. Tikkanen et al. showed that HL activity falls significantly in healthy premenopausal women during the luteal phase of the menstrual cycle, when endogenous estradiol levels are highest (58). HL activity decreases progressively across pregnancy as estradiol levels increase (59). The fall in endogenous estrogen with menopause is associated with a rise in HL activity (60, 61). A study of endogenous testosterone production in prepubescent boys showed a rise in androgen levels associated with a significant increase in HL activity (62).

HL activity decreases significantly with exogenous oral estrogens (18, 63) and increases 3-fold with exogenous androgenic steroids (64, 65). Estrogen replacement therapy in postmenopausal women acutely reduces HL activity (18, 19, 66). Colvin et al. demonstrated that orally administered micronized estradiol suppressed HL activity and increased HDL in a dose-dependent manner (64, 67). Synthetic progestational agents with androgenic activity (52, 68) and anabolic steroids both increase HL activity and lower HDL (64, 65, 67). Somekawa et al. recently showed that the HL promoter polymorphism (−514) had no effect on the lipid response to hormone replacement therapy in postmenopausal women. The relationship may have been obscured by the fact that the conjugated estrogen and medroxyprogesterone acetate were given continuously (daily), with each having opposite effects on HL activity (69). It is believed that the influence of sex steroids on serum HDL cholesterol occurs through the action of HL activity. Recent in vitro studies on the *LIPC* promoter in HepG2 cells support an inhibitory action by estradiol that is mediated by an AP1 response element in the promoter (70).

The higher amount of IAF in men (71) also accounts for part of the gender dimorphism in HL activity. Women tend to store fat in the gluteo-femoral (subcutaneous) region while men store fat in the abdominal (intraabdominal) depot. IAF is an important determinant of HL activity (43, 44), independent of total body fat content, in both men and women. Carr et al. showed that IAF accounts for a portion of the gender difference in HL activity, but there was still a residual difference in HL activity not accounted for by visceral obesity or the HL gene promoter polymorphism (50). Similarly, Despres et al. failed to eliminate the differences in lipoproteins between men and women after statistical adjustment for both HL and lipoprotein lipase, implying that other factors (such as body fat distribution) accounted for residual gender differences in plasma lipid concentrations (46).

Gene-diet interaction in regulation of HL activity

Saturated fat intake is associated with changes in lipoprotein particle heterogeneity that might be mediated by changes in HL activity in humans. With decreasing saturated fat intake, HDL_2 (72, 73) and LDL (74, 75) cholesterol levels fall with a decrease in LDL peak buoyancy, size, and cholesterol content per particle (74, 75). Saturated fat intake has been shown to be inversely related to HL activity (74). Thus, large, more buoyant LDL and larger HDL_2 particles seen with higher saturated fat intake have been proposed to be secondary to decreases in HL activity (74).

Interestingly, dietary fat intake has recently been shown to significantly modify the association between the *LIPC* −514 C to T polymorphism and HDL cholesterol concentrations (76). In the Framingham Study, the T allele was correlated with higher HDL cholesterol concentrations only in individuals who usually consume a low-fat diet. In contrast, the TT genotype was associated with lower HDL cholesterol levels in individuals who usually consume a high-fat diet. Similar results were observed when HDL_2 cholesterol was the variable. This gene-diet interaction was observed for saturated and monounsaturated fat, but not for polyunsaturated fat. The mechanism for this interaction is unclear.

The *LIPC* promoter polymorphism interacts with lipid-lowering intervention in determining HDL and LDL subclasses and CAD regression

A significant fraction of patients undergoing lipid-lowering treatment for both primary and secondary CAD prevention experience little or no benefit. Factors other than decrease in LDL cholesterol and increase in HDL are likely to be involved in determining outcome. One such factor is the change in HL activity upon treatment. In the Familial Atherosclerosis Treatment Study trial, treatment of men with established CAD and dyslipidemia with statin/colestepol or niacin/colestepol resulted in a decrease

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in HL activity and an increase in LDL particle buoyancy (77). Importantly, the change in LDL buoyancy, resulting from the decrease in HL activity, was most strongly associated with disease progression. Furthermore, the *LIPC* −514 C→T polymorphism significantly predicted coronary stenosis regression during intensive lipid-lowering treatment (78). This association appears to be mediated by the modulating effect of this polymorphism on specific drug-induced changes in lipoprotein metabolism. The *LIPC* polymorphism has no significant impact on the lipoprotein pathway leading to changes in LDL and apoB levels. However, the *LIPC* genotype is strongly associated with LDL buoyancy and CAD regression. Homozygous *CC* patients exhibited a greater decrease in HL activity and a greater increase in LDL buoyancy with lipid-lowering therapy as compared with both CT and TT carriers. Therefore, in patients with the *CC* genotype, the combination of decreasing LDL cholesterol and apoB concentrations and increasing HDL_2 cholesterol levels and LDL buoyancy may account for the significantly greater angiographic regression of coronary stenosis seen in this group as compared with CT and TT individuals.

CONCLUSIONS

During the past decade, robust evidence has been provided to support a key role of HL in remnant lipoprotein, LDL, and HDL remodeling. In addition to its lipolytic activity, a role of HL as ligand, independent of its enzymatic activity, has been recently suggested, which affects both remnant lipoproteins and HDL levels. HL has emerged as key player in modulating LDL and HDL subclass distribution and the atherogenic lipoprotein profile. *1*) Higher HL activity is associated with small, dense, and more atherogenic LDL particles as well as with low HDL_2 cholesterol. This may impact on both atherosclerotic plaque formation and progression as well as on the rate of reverse cholesterol transport. *2*) Complete HL deficiency is associated with accelerated CAD through the accumulation of atherogenic remnant and TG-rich LDL-like particles. Impaired remnant catabolism may also account for the increased CAD risk in these patients. *3*) HL activity is influenced by a polymorphism (T-514C) in the *LIPC* promoter, gender, IAF, and dietary fat intake. Significant interactions exist between the *LIPC* promoter polymorphism and IAF and fat intake. *4*) A significant benefit of lipid-lowering therapy in CAD patients is the decrease in HL activity resulting in the increased prevalence of large, buoyant LDL particles. The *LIPC* −514 C→T polymorphism modulates this response. Patients with the *CC* genotype receive the greatest clinical benefits from intensive therapy because they tend to have high HL activity and small, dense LDL. *5*) HL may be both a proatherogenic and antiatherogenic factor [review in ref. (4)] (depending on the balance between production of small, dense LDLs and the rate or reverse cholesterol transport. High levels of HL may be atherogenic only in the presence of high concentrations of LDLs that are converted to small, dense LDLs. When LDL levels are low, high HL activity may be antiatherogenic due to accelerated reverse cholesterol transport. Two common syndromes with central obesity and insulin resistance where elevated HL is associated with increased small, dense LDL particle numbers are Type 2 diabetes and familial combined hyperlipidemia (79).

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