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Hepatic lipase activity is lower in African American men than in white American men: effects of 5′ flanking polymorphism in the hepatic lipase gene (*LIPC*)

Gloria Lena Vega,* Luther T. Clark,† Aylmer Tang,† Santica Marcovina,§ Scott M. Grundy,* and Jonathan C. Cohen[1,*]

The Center for Human Nutrition,* Departments of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9052; The State University of New York Health Science Center at Brooklyn,† Brooklyn, NY 11203; and Department of Medicine and Northwest Lipid Research Laboratories,§ The University of Washington, Seattle, WA 98103

Abstract Plasma high density lipoprotein cholesterol (HDL-C) concentrations are higher in African American men than in white men, but the mechanism(s) responsible for this ethnic difference has not been elucidated. This study examined the relationship between hepatic lipase activity, plasma HDL-C concentrations, and a hepatic lipase polymorphism (−514T) in African American and white American men. Consistent with previous reports, plasma HDL-C concentrations were significantly higher in African American men than in white American men. Mean post-heparin plasma hepatic lipase activity was significantly lower in African American than in white American men (27 ± 12 vs. 44 ± 17 mmol · $h^{-1} \cdot l^{-1}$, $P < 0.001$). The −514T hepatic lipase allele was associated with low hepatic lipase activity in both populations, and was 3-fold more common among African Americans than white Americans. Taken together, these data suggest that genetic differences in hepatic lipase activity contribute to the differences in plasma HDL-C concentrations between African American men and white American men.—**Vega, G. L., L. T. Clark, A. Tang, S. Marcovina, S. M. Grundy, and J. C. Cohen.** Hepatic lipase activity is lower in African American men than in white American men: effects of 5′ flanking polymorphism in the hepatic lipase gene (*LIPC*). *J. Lipid Res.* 1998. **39:** 228–232.

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Epidemiological studies have shown that plasma high density lipoprotein cholesterol (HDL-C) concentrations are higher in African American men than in white American men (1–4). This ethnic difference in plasma HDL-C concentrations cannot be accounted for by environmental factors, and is therefore likely to be of genetic origin (2). Interestingly, the difference is specific to men, and reflects differences in the magnitude of the pubertal decrease in plasma HDL-C concentrations that occurs during puberty in boys (1, 4). The pubertal decrease in plasma HDL-C concentrations appears to be due to an androgen-mediated increase in the activity of hepatic lipase, an enzyme that catalyzes the hydrolysis of HDL triglycerides and phospholipids (5). Androgen administration leads to a dose-dependent increase in hepatic lipase activity (6, 7) and decreases plasma HDL-C concentrations in men and women (8–11). Differences in the responsiveness of hepatic lipase to androgens, therefore, could explain the sex-specific differences in plasma HDL-C concentrations between African Americans and white Americans.

Recently we identified a hepatic lipase allele that is associated with increased plasma HDL-C concentrations in men, but not in women (12). The allele (designated −514T) is defined by four linked polymorphisms in the 5′ flanking region of the gene, and has a frequency of 0.15 in white Americans. Plasma HDL-C concentrations were slightly higher in white men who were heterozygotes for the −514T allele, and appreciably higher in men who were −514T homozygotes. As the −514T allele leads to increased plasma HDL-C concentrations in men only, an increased frequency of this allele in African Americans could explain the sex-specific increase in plasma HDL-C concentrations in this population. To test this hypothesis, we compared plasma HDL-C concentrations, post-heparin plasma hepatic lipase activities, and −514T allele frequencies in African American and white American men.

Abbreviations: HDL-C, high density lipoprotein cholesterol.

[1]To whom correspondence should be addressed.

METHODS

The study was approved by the Internal Review Boards at the University of Texas Southwestern Medical Center and the State University of New York Health Science Center.

Subjects

Two independent groups of men were recruited for this study. Plasma HDL-C concentrations, post-heparin plasma hepatic lipase activities, and *LIPC* genotypes were assayed in 43 African Americans and 45 white Americans aged 20 to 40 years who were medical students and staff of the State University of New York Health Science Center (Group 1). *LIPC* genotypes were determined in 54 African Americans and 60 white Americans recruited at a health fair sponsored by the Dallas Firefighters Association (Group 2).

Assay of plasma lipoproteins

Plasma concentrations of cholesterol and triglyceride were measured enzymatically using commercial reagents. Plasma HDL-C concentrations were measured by sodium phosphotungstate (0.55 mm) precipitation.

Assay of post-heparin plasma hepatic lipase activity

Hepatic lipase activity was measured in post-heparin plasma as described previously (13).

Assay of *LIPC* genotypes

The *LIPC* polymorphisms located at −250, −514, and −763 were assayed by PCR amplification and restriction digestion as described previously (12).

Statistical analysis

Median plasma HDL-C concentrations and hepatic lipase activities of African American and white men were compared using the Wilcoxon rank test. The correlation between plasma HDL-C concentrations and hepatic lipase activity was calculated using Pearson's method. The frequency of −514T homozygotes was compared in the two populations using Fisher's exact test. The observed frequencies of the −514C and −514T alleles were compared with the frequencies expected under Hardy-Weinberg equilibrium by χ^2 tests.

RESULTS

Plasma HDL-C concentrations and hepatic lipase activities in African American and white American men

Mean plasma HDL-C concentrations were significantly higher in African American than in white American men (**Table 1**). Mean post-heparin plasma hepatic lipase activity was markedly lower in African American men than in white men (Table 1). Hepatic lipase activity was less than 20 mmol·h^{-1}·l^{-1} in 12 of the 43 African Americans studied (28%). and less than 40 mmol·h^{-1}·l^{-1} in 39 (91%). Only 1 African American man (2%) had a hepatic lipase activity greater than 50 mmol·h^{-1}·l^{-1}. In contrast, none of the 45 whites in the study had hepatic lipase activities below 20 mmol·h^{-1}·l^{-1}; 20 (44%) had activities below 40 mmol·h^{-1}·l^{-1}; and 16 (35%) had hepatic lipase activities exceeding 50 mmol·h^{-1}·l^{-1}. Plasma HDL-C concentrations and hepatic lipase activities were inversely correlated both in African Americans ($r = -0.32$, $P < 0.036$) and whites ($r = -0.42$, $P < 0.004$). Mean plasma HDL-C concentrations were similar in the 27 African Americans and 20 whites whose hepatic lipase activities were between 20 and 40 mmol·h^{-1}·l^{-1} (46 ± 11 vs. 45 ± 9, $P > 0.8$).

TABLE 1. Plasma lipids and HDL-C concentrations in African American and white American men

	African American Men	White Men
n	43	45
Number of smokers	12	6
Height (in)	71 ± 3	71 ± 3
Body weight (lbs)	180 ± 24	186 ± 34
Body mass index (kg/m^2)	25 ± 4	26 ± 4
Plasma cholesterol (mg/dl)	171 ± 36	174 ± 33
Plasma triglyceride (mg/dl)	80 ± 50	95 ± 49
Plasma HDL-C (mg/dl)	46 ± 11[a]	41 ± 10
Hepatic lipase activity (mmol·h^{-1}·l^{-1})	27 ± 12[b]	44 ± 17

Values are means ± SD from individuals recruited in New York (Group 1).
[a] $P < 0.025$, Wilcoxons rank sum test.
[b] $P < 0.0001$, Wilcoxons rank sum test.

Frequency of the −514T allele in African Americans and white Americans

DNA samples were obtained from 42 of the African American and 41 of the white men recruited in New York. In this group, the frequency of the −514T allele was significantly higher in African Americans (0.52) than in white Americans (0.17, $P < 0.0001$). Essentially identical results were observed among firefighters recruited in Dallas (Group 2), where the frequency of the −514T allele was 0.53 in African Americans and 0.18 in white Americans ($P < 0.0001$). In both groups of African Americans and white Americans, the relative frequencies of the −514C and −514T alleles were consistent with Hardy-Weinberg equilibrium (**Table 2**). In the 40 African American alleles examined, complete linkage disequilibrium was observed between the polymorphisms at −250, −514, and −763.

TABLE 2. *LIPC* allele frequencies in African American and white American men

Genotype	African American Men		White Men	
	Observed	Expected[a]	Observed	Expected[a]
Group 1				
CC	10	10	28	28
TC	20	21	12	12
TT	12[c]	12	1	1
Group 2				
CC	11	12	39	41
TC	29	27	21	17
TT	14[b]	15	0	2

Group 1 was recruited in New York. Group 2 was recruited in Dallas.

[a]Numbers are rounded to the nearest integer value. Observed allele frequencies were not different from expected for each group ($P > 0.9$ χ^2 test).

[b]$P < 0.0001$ for frequency of TT genotype in African Americans vs. whites.

TABLE 3. Postheparin plasma hepatic lipase activities and *LIPC* genotypes in African American and white American men

	African Americans	Whites
All[a]	27 ± 12 (42)[b]	45 ± 16 (41)
CC	32 ± 10 (10)[c]	51 ± 15 (28)[e]
CT	26 ± 12 (20)[d]	37 ± 12 (12)
TT	24 ± 13 (12)	35

Values ($mmol \cdot h^{-1} \cdot l^{-1}$) are means ± SD from individuals recruited in New York (Group 1). Sample sizes are given in parentheses.

[a]All individuals from whom *LIPC* genotype data were available.

[b]$P < 0.0001$ versus whites, Wilcoxons test.

[c]$P < 0.001$ versus whites; $P < 0.025$ versus African Americans with CT genotype.

[d]$P < 0.005$ versus whites.

[e]$P < 0.01$ versus whites with CT genotype.

Effects of *LIPC* genotype on hepatic lipase activities in African American and white American men

In both African Americans and whites, hepatic lipase activity was significantly higher in CC homozygotes than in CT heterozygotes (**Table 3**). Only 1 white American was homozygous for the −514T allele. In African Americans, mean hepatic lipase activity was slightly lower in TT homozygotes than in CT heterozygotes, but this difference did not reach significance at the 0.05 confidence level. When individuals were grouped by race and *LIPC* genotype, African Americans with the CC or CT genotype had significantly lower hepatic lipase activity than did white Americans with the corresponding genotypes. The sample size precluded a comparison of the TT genotype in the two ethnic groups.

DISCUSSION

There is considerable evidence that hepatic lipase activity is an important determinant of plasma HDL-C concentrations. Clinical studies have consistently found an inverse relationship between hepatic lipase activity measured in post-heparin plasma and plasma HDL-C concentrations (13–17), and genetic studies have indicated linkage between the gene encoding hepatic lipase and plasma HDL-C concentrations in white Americans (12, 18). In the present study, we have evaluated the relationship between hepatic lipase activity, plasma HDL-C concentrations, and hepatic lipase genotypes in African American and white American men. Consistent with previous reports (1–4), plasma HDL-C concentrations were significantly higher in African American men than in white American men in this study. In addition, two novel observations were made. First, hepatic lipase activity is significantly lower in African American than in white American men. Second, the −514T hepatic lipase allele, which is associated with low hepatic lipase activity and increased plasma HDL-C concentrations, is far more common among African Americans than among white Americans. Taken together, these data suggest that genetic differences in hepatic lipase activity contribute to the differences in plasma HDL-C concentrations between African American and white Americans.

Although the difference in plasma HDL-C concentrations between African American and white American men has been well established, the mechanism(s) responsible for this difference has not been elucidated. Hepatic lipase activities in African American men have not been reported previously. The present data indicate that hepatic lipase activity is markedly lower in African American men than in white American men. In both groups, plasma HDL-C concentrations were inversely related to post-heparin plasma hepatic lipase activities. Among men with post-heparin plasma hepatic lipase activities between 20 and 40 $mmol \cdot h^{-1} \cdot l^{-1}$, no ethnic difference in plasma HDL-C concentrations was observed. This finding suggests that the difference in plasma HDL-C concentrations between African American and white men can be accounted for in large part by differences in hepatic lipase activity.

Recently, we have identified an allele of hepatic lipase (defined by a T 514 bases upstream of the transcription start site) that is associated with increased plasma HDL-C concentrations and low hepatic lipase activity in white men (12). In the current study, we sought to determine whether the low hepatic lipase activities in African American men are due to an increased frequency of this allele. *LIPC* genotypes were assayed in two independent groups of African American and white men. In both groups, the −514T allele of *LIPC* was 3-fold more common in African Americans

than in whites. As we observed previously in white Americans (12), the polymorphism at −514 was in complete linkage disequilibrium with two other polymorphisms in the 5′ flanking region of *LIPC*, indicating that this allele arose early in human evolution. In African Americans and in whites, hepatic lipase activities were highest in men who were homozygous for the C allele, lower in CT heterozygotes, and lowest in TT homozygotes. This finding indicates that the increased frequency of the −514T allele contributes to low post-heparin plasma hepatic lipase activities observed in African American men. Interestingly, however, post-heparin plasma hepatic lipase activities were lower in African American men than in white men, even among individuals of the same *LIPC* genotype. Therefore, the increased frequency of the −514T allele in African American men does not fully account for the ethnic frequency of the ethnic difference in post-heparin plasma hepatic lipase activity. This difference may be due to other, as yet unidentified polymorphisms in *LIPC*, or to factors that influence the synthesis or secretion of the hepatic lipase protein.

Although our data indicate that the difference in plasma HDL-C concentrations between African American and white men reflects ethnic differences in hepatic lipase activity, it is possible that HDL-C concentrations and hepatic lipase activities are jointly influenced by a third factor that affects both of these parameters independently, and that the two are not causally related. Several lines of evidence support a direct effect of hepatic lipase on plasma HDL-C concentrations, however. Genetic deficiency of hepatic lipase is associated with increased plasma HDL-C concentrations (19), whereas administration of pharmacological doses of androgens leads to reciprocal changes in hepatic lipase activity and plasma HDL-C concentrations (6, 7). In vitro studies indicate that HDL is a substrate for hepatic lipase (20, 21). Finally, overexpression of human hepatic lipase in transgenic animals leads to decreased plasma HDL-C concentrations (22, 23). Therefore, while we cannot formally exclude the possibility that the low hepatic lipase activity observed in African American men is not directly related to their increased plasma HDL-C concentrations, a causal relationship between the two parameters seems more likely. Accordingly, we conclude that low hepatic lipase activity leads to increased plasma HDL-C concentrations in African American men. The low hepatic lipase activities in African American men are likely to be genetically determined, and are due in part to the high frequency of the −514T allele in this population.

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