Elevated hepatic lipase activity and low levels of high density lipoprotein in a normotriglyceridemic, nonobese Turkish population

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Abstract **Low levels of high density lipoprotein cholesterol (HDL-C) are associated with increased risk of coronary heart disease and, in the United States, are often associated with hypertriglyceridemia and obesity. In Turkey, low HDL-C levels are highly prevalent, 53% of men and 26% of women having HDL-C levels <35 mg/dl, in the absence of hypertriglyceridemia and obesity. In this study to investigate the cause of low HDL-C levels in Turks, various factors affecting HDL metabolism were assessed in normotriglyceridemic Turkish men and women living in Istanbul and in non-Turkish men and women living in San Francisco. Turkish men and women had significantly lower HDL-C levels than the San Francisco men and women, as well as markedly lower apolipoprotein A-I levels (25 and 39 mg/dl lower, respectively). In both Turkish and non-Turkish subjects, the mean body mass index was <27 kg/m^2, the mean triglyceride level was <120 mg/dl, and the mean total cholesterol was 170–180 mg/dl. The mean hepatic triglyceride lipase activity was 21% and 31% higher in Turkish men and women, respectively, than in non-Turkish men and women, and remained higher even after subjects with a body mass index >50th percentile for men and women in the United States were excluded from the analysis. As no dietary or behavioral factors have been identified in the Turkish population that account for increased hepatic triglyceride lipase activity, the elevation most likely has a genetic basis.**—Bersot, T. P., G. L. Vega, S. M. Grundy, K. E. Palaoğlu, P. Atagündüz, S. Özbayrakçi, O. Gökdemir, and R. W. Mahley. **Elevated hepatic lipase activity and low levels of high density lipoprotein in a normotriglyceridemic, nonobese Turkish population.** ***J. Lipid Res.*** 40: **432–438.**

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In the United States and Europe, low levels of high density lipoprotein cholesterol (HDL-C), defined as HDL-C <35 mg/dl, affect about 15% of men and 5% of women (1). Despite the high prevalence of premature coronary heart disease among affected persons, little is known about the pathophysiology of low HDL-C (2–6). The complex interaction among genetic and behavioral factors that influence HDL-C levels partially accounts for this lack of knowledge. Smoking, obesity, exercise, types and amounts of dietary fat, and ethanol consumption are behavioral factors that affect HDL-C levels (7–13). Genetic syndromes associated with low HDL-C levels include various forms of primary hypertriglyceridemia, type 2 diabetes mellitus, isolated low HDL-C, and mutations in the genes encoding apolipoprotein (apo) A-I, lecithin:cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP) (5, 14, 15). Variability in hepatic triglyceride lipase (HTGL) and lipoprotein lipase (LPL) activities also affects HDL-C levels in the United States (15). Allelic variations at the apoA-I and HTGL loci appear to account for as much as half of the interindividual variation in HDL-C levels (16).

These diverse factors have made it difficult to identify a large cohort of subjects in the United States with isolated low HDL-C caused by an allelic variant of a specific gene. The Turkish Heart Study, a recently published survey of heart disease risk factors in Turkey, documented that Turks have the greatest prevalence of low HDL-C of any country or ethnic group in which plasma lipid levels have been extensively characterized (17). In Turkey, 53% of men and 26% of women have HDL-C levels below 35 mg/

Abbreviations: apo, apolipoprotein; BMI, body mass index; CETP, cholesteryl ester transfer protein; HDL-C, high density lipoprotein cholesterol; HTGL, hepatic triglyceride lipase; LCAT, lecithin:cholesterol acyltransferase; LDL-C, low density lipoprotein cholesterol; LpA-I, a subfraction of HDL containing apoA-I but not apoA-II; LpA-I/A-II, a subfraction of HDL containing both apoA-I and apoA-II; LPL, lipoprotein lipase; PTA, phosphotungstic acid.

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dl. The prevalence of low HDL-C levels is consistent irrespective of geographic location or substantial regional variation in the type of dietary fat and is not attributable to behavioral factors (smoking, exercise, or ethanol consumption) that commonly modulate HDL-C levels. Moreover, triglyceride levels of Turks with low HDL-C levels are not significantly elevated. Thus, the low HDL-C levels in this population may represent an example of isolated low HDL-C (17).

To investigate the cause of low HDL-C levels in the Turkish population, we assessed factors affecting HDL metabolism, including HTGL, LPL, CETP, and LCAT activities, in a cohort of Turkish subjects residing in Istanbul and compared the results with those of control subjects residing in San Francisco, CA.

MATERIALS AND METHODS

Study subjects

We recruited healthy Turkish subjects who were employees, or relatives or friends of employees, of the Koç American Hospital, Istanbul. The participants were screened to exclude those with triglycerides >200 mg/dl and those with chronic medical problems including diabetes mellitus, coronary heart disease, or hypertension. Patients using hypolipidemic drugs, hormone replacement, oral contraceptives, β-blockers, and thiazide diuretics were also excluded. There were 98 men and 116 women, aged 18–81 and 16–68 years, respectively.

The control subjects were healthy non-Turkish San Francisco residents with triglyceride levels less than 200 mg/dl. There were 31 white men and 29 white women, aged 26–48 and 24–50 years, respectively. None of the control subjects used any medication regularly. As the Turkish and non-Turkish participants represented different ethnic populations, selection of non-Turkish subjects in San Francisco for comparison with Turks in Istanbul was made primarily on the basis of similarity in body mass index (BMI). This selection allowed for a comparison between two populations in which the factor of overweight was eliminated (see Results section).

All participants gave informed consent for the study, which was approved by the Committee on Human Research, University of California, San Francisco. Two blood samples were obtained, one before and one 15 min after intravenous injection of heparin (75 IU/kg: Elkins-Sinn, Cherry Hills, NJ); all subjects fasted for 12 h before phlebotomy. The first sample was used to measure plasma lipid, lipoprotein cholesterol, apoA-I, and apoB concentrations, as well as CETP and LCAT activities. The second sample was used to measure LPL and HTGL activities; the HTGL concentration was determined in a subset of samples. To prevent coagulation and preserve the samples, 10 μl of a solution containing the following substances was added to each tube to achieve the indicated final plasma concentrations: EDTA, 1 mg/ml; chloramphenicol, 0.005%; gentamicin sulfate, 0.005%; sodium azide, 0.01%; and aprotinin, 100 IU/ml. Blood samples were immediately placed on ice, and the plasma was separated from the cells within 2 h after phlebotomy. Aliquots for the various assays were frozen at −70°C.

Laboratory procedures

The plasma total cholesterol, triglyceride, and HDL-C concentrations of Turkish subjects were measured in the certified lipid reference laboratory (17) of the Koç American Hospital in Istanbul. The HDL-C levels were measured after precipitation of very low density lipoproteins (VLDL) and low density lipoproteins (LDL) with phosphotungstic acid (PTA) and magnesium (Mg). Kits for the lipid assays were from Boehringer-Mannheim (Mannheim, Germany), and a Hitachi multichannel analyzer was used for the colorimetric enzymatic determinations (Monotest Cholesterol, CHOD-PAP; Peridochrom Triglyceride, GPO-PAP). The LDL-C values were estimated by the Friedewald calculation (18).

Lipid determinations in control subjects were performed at the Gladstone Institute of Cardiovascular Disease. Plasma total cholesterol and triglyceride concentrations were determined with an Abbott Spectrum high-performance diagnostic system and standards in aqueous solution (New England Reagent Laboratory). The HDL-C levels were measured after precipitation of apoB-containing lipoproteins with PTA/Mg and were calibrated with HDL-C standards (Abbott Laboratories) (19). HDL-C levels measured on the same samples in Istanbul and San Francisco by the same technique (PTA/Mg precipitation) were compared by linear regression analysis and the coefficient of variation, *r*, was 0.91.

Plasma concentrations of apoA-I and apoB were measured by previously described electroimmunoassays, each with inter- and intra-assay variations of less than 5% (20). The concentrations of the LpA-I and LpA-I/A-II subfractions were determined by electroimmunoassay as previously described (21).

Plasma samples for assays of LCAT, CETP, HTGL, and LPL activities and HTGL mass were packed in dry ice and transported by courier from Istanbul to the United States, arriving within 24 h after departure. Assays for enzymatic and transfer protein activities were performed at the Center for Human Nutrition, University of Texas Southwestern Medical School, Dallas, TX.

The CETP and LCAT activities were measured isotopically, as previously detailed (22). These activity measurements correlate with the protein concentrations and are not intended as precise estimates of in vivo activity (22, 23). Briefly, CETP activity is reported as percent transfer of tritiated cholesteryl ester from a donor lipoprotein (HDL_3) to an acceptor lipoprotein (LDL). Donor and acceptor lipoproteins were prepared from pooled plasma of healthy volunteers (23). The CETP activity was estimated by adding a small aliquot of plasma from a subject to the mixture of donor and acceptor lipoproteins. After incubation for 16 h at 37°C, the mixture was placed on ice for 15 min to stop the reaction. Acceptor LDL were precipitated, and dpm from donor HDL_3 were determined by counting an aliquot of the supernatant. Appropriate blanks were included in the assay, and the same quality control was used in all assays (22, 23). The intra- and interassay coefficients of variation were less than 6% (23).

The LCAT activity assays were performed as previously described (22). Proteoliposomes containing apoA-I and tritiated unesterified cholesterol were preincubated with 2% bovine serum albumin in assay buffer (10 mm Tris base, 150 mm NaCl, 1 mm disodium EDTA, pH 7.4) at 37°C for 30 min. After precipitation of apoB-containing lipoproteins with PTA/Mg, 4 μl of the plasma supernatant, 50 μl of the proteoliposome mixture, and 25 μl of 43 mm β-mercaptoethanol were incubated at 37°C for 30 min to measure LCAT activity. The reaction in each sample was stopped by adding 1.0 ml of 0.5% digitonin in 5% ethanol followed by 75 μl of 0.75% cholesterol in 95% ethanol.

The HTGL and LPL activities were measured in postheparin plasma as previously described (24). The LPL activity was measured in a small aliquot of plasma in the presence of exogenous apoC-II after inhibition of HTGL by sodium dodecyl sulfate. The HTGL activity was measured in a separate aliquot of postheparin plasma after inhibition of LPL by high-ionic-strength NaCl. A gum arabic-stabilized artificial emulsion containing a mixture of nonradioactive and radioactive triolein was the assay substrate used to measure the activities of both enzymes. After incubation of the samples at 37°C, the hydrolysis reactions were stopped by

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placing the tubes in ice and extracting the liberated free fatty acids with organic solvents. The released radioactive free fatty acids were quantified, and the enzyme activities were expressed as millimoles of free fatty acids released per hour per liter of plasma. The intra- and interassay coefficients of variation were less than 5%.

In a subset of 80 Turkish subjects, the HTGL concentration was determined with a sandwich immunoassay described previously (25). The assays were performed by Dr. A. Bensadoun (Cornell University, Ithaca, NY).

Statistical analysis

The data are summarized as the mean ± standard deviation (SD). Nonparametric statistical analysis was used to compare groups. Means were compared by the Mann-Whitney method. Despite inequalities in group size, power tests indicated that there were adequate numbers of subjects for valid statistical comparison. Differences in rank sums were considered significant at a *P* value of 0.05 or less. Spearman correlation coefficients were used to assess associations between independent variables. All analyses were performed with BMDP statistical software.

The aim of the study was to determine whether there was an inherent difference between the two populations in the various metabolic factors known to influence HDL-C levels. No attempt was made to assess the relative contributions of those factors to the variation in HDL-C levels within each population. Instead, the relative magnitudes of these factors in the two populations were compared and, when significant differences were found by one-way analysis of variance, analysis of covariance was applied to determine whether those differences were confounded by other factors (i.e., age, BMI, and triglyceride levels).

RESULTS

The characteristics of the four groups of subjects in this study are presented in **Table 1**, and the statistical significance of differences in these characteristics is given in **Table 2**. The mean ages of the groups were similar. The BMI was somewhat higher in Turkish than in non-Turkish subjects, but only the difference between the male groups was statistically significant. Both HDL-C and total apoA-I concentrations were significantly lower in Turkish men and women than in the control subjects. Plasma triglyceride levels were significantly higher in both groups of Turkish subjects, but the mean triglyceride level was below 120 mg/dl in all groups. Analysis of covariance was performed to assess the effects of triglyceride level, BMI, and age on differences in HDL-C levels between Turks and non-Turks. After adjustment for these covariates, the differences in HDL-C levels between groups remained statistically significant in both men and women (**Table 3**). Assumptions of non-zero and equal slopes were appropriately assessed. Because there was a very slight curvilinear relationship between triglyceride and HDL-C levels, the analysis was also performed after log transformation of the dependent variable. The results of this analysis were essentially identical to those of the original analysis.

TABLE 2. Statistical significance (Mann-Whitney *P* value) of differences in various characteristics between Turks and non-Turks

Characteristic	Non-Turkish Men Versus Turkish Men	Non-Turkish Women Versus Turkish Women
Age	0.19	0.67
BMI	0.02	0.41
Total cholesterol	0.5	0.29
Triglycerides	0.0001	0.006
LDL-C	0.53	0.0007
HDL-C	0.0001	0.00001
Non-HDL-C	0.09	0.001
Total apoB	0.17	0.004
Total apoA-I	0.00001	0.00001
CETP	0.08	0.09
LCAT	0.73	0.00001
LPL	0.24	0.0002
HTGL	0.01	0.0002
HTGL/LPL	0.02	0.00001

Total cholesterol levels did not differ among the groups. LDL-C levels were not different between the two male groups, but were higher in Turkish women than in non-Turkish women, as were total apoB levels (Tables 1 and 2).

The LPL activities were significantly different in the two groups of women but not in the two groups of men (Tables

TABLE 1. Characteristics of Turkish and non-Turkish control subjects

Characteristic	Men: Turks (n = 98)	Men: Non-Turks (n = 31)	Women: Turks (n = 116)	Women: Non-Turks (n = 29)
Age (years)	39 ± 12	35 ± 7	36 ± 11	36 ± 7
BMI (kg/m^2)	25.8 ± 3.3	24.6 ± 3.0	24.8 ± 5.3	23.6 ± 3.9
Total cholesterol (mg/dl)	178 ± 42	169 ± 32	182 ± 39	173 ± 28
Triglycerides (mg/dl)	119 ± 46	83 ± 43	90 ± 36	71 ± 30
LDL-C (mg/dl)	117 ± 40	107 ± 32	122 ± 36	99 ± 25
HDL-C (mg/dl)	37 ± 9	45 ± 11	43 ± 9	58 ± 15
Non-HDL-C (mg/dl)	141 ± 44	124 ± 37	139 ± 39	115 ± 26
Total apoB (mg/dl)	92 ± 29	98 ± 24	88 ± 24	75 ± 24
Total apoA-I (mg/dl)	107 ± 19	132 ± 30	117 ± 25	153 ± 25
CETP (% transfer)	27.6 ± 7.9	29.1 ± 2.8	27.7 ± 7.9	29.2 ± 5.3
LCAT (nmol/ml/h)	251 ± 51	254 ± 39	242 ± 52	302 ± 45
LPL (mmol/ml/h)	11.5 ± 4.8	12.5 ± 4.4	10.2 ± 4.1	13.1 ± 5.0
HTGL (mmol/ml/h)	48.1 ± 16.1	38.8 ± 13.9	35.1 ± 12.3	26.7 ± 7.9
HTGL/LPL	4.8 ± 2.5	3.8 ± 2.5	3.9 ± 2.0	2.5 ± 1.9

All values are mean ± SD.

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TABLE 3. Analysis of covariance assessing the effects of plasma triglyceride, BMI, and age on differences in HDL cholesterol between Turks and non-Turks

	Mean HDL Cholesterol Level					
	Men			Women		
	Turks	Non-Turks	*P*	Turks	Non-Turks	*P*
	mg/dl			*mg/dl*		
Unadjusted levels	37	45	<0.0001	43	58	<0.0001
Adjusted for plasma TG	38	43	<0.016	43	56	0.0001
Adjusted for TG and BMI	38	43	<0.017	43	57	0.0001
Adjusted for TG, BMI, and age	37	43	<0.015	43	56	0.0001
Adjusted for BMI and age	37	44	<0.0004	43	57	0.0001

TG, triglycerides.

1 and 2). The CETP activities were lower in the Turkish subjects, but the differences were not significant. The LCAT activities were nearly identical except in non-Turkish women, who had a higher mean LCAT activity than the other three groups. The mean HTGL activity was 24% and 31% higher in Turkish men and women, respectively, than in non-Turkish men and women. These differences were statistically significant and stand out as a distinguishing characteristic of the Turkish subjects. Analysis of covariance revealed that age was not a confounding variable for differences in HTGL activity.

The increased HTGL activity in the Turkish subjects in this study might reflect an HTGL gene polymorphism affecting gene expression. If gene expression were increased, the HTGL concentration would increase commensurately with the increase in HTGL activity. To assess this possibility, we measured HTGL concentration and activity in the same postheparin plasma sample of 80 Turkish subjects. The mean HTGL concentration for 37 men was 373 ± 124 ng/dl and for 43 women was 243 ± 97 ng/dl. Regression analysis showed a strong correlation between the HTGL concentration and HTGL activity levels ($r = 0.71$; 95% confidence interval = 0.58–0.78; $P < 0.05$). These data suggest that the higher HTGL activity in the Turkish population is due to an increase in HTGL concentration.

The concentrations of two HDL subfractions, LpA-I and LpA-I/A-II, in the Turkish subjects are shown in **Table 4**. Comparisons of HTGL activity and LpA-I level with other related variables are shown in **Table 5**. In women, but not in men, HTGL activity correlated significantly and inversely with HDL-C levels. However, in both men and women, HTGL activities correlated inversely with LpA-I levels and positively with BMI. The HTGL activity also correlated positively with the triglyceride level in women but not in men. In women only, there was a significant positive correlation between the LpA-I level and LPL activity. Importantly, the LpA-I level correlated inversely with HTGL activity in both men and women. The LpA-I level correlated significantly and negatively with the triglyceride level and BMI in women but correlated significantly only with BMI in men.

To exclude possible effects of the slightly higher BMI in Turks on HTGL activity and LpA-I levels, we reanalyzed the data after excluding subjects with BMI >50th percentile for men and women in the United States [26 kg/m^2 for men and 25 kg/m^2 for women (26)]. The results of this analysis are shown in **Table 6** and **Table 7**. Nonobese Turkish women were 2–5 years younger than the other groups. However, the BMIs in the two groups of men were similar, as were those in the two groups of women. There were no differences in total cholesterol between groups. The plasma LDL-C and apoB concentrations were not different in the two male groups, but were higher in nonobese Turkish women than in non-Turkish women. All groups had normal triglyceride levels (below 115 mg/dl), but both Turkish men and women had significantly higher triglyceride levels than their respective non-Turkish controls.

Among nonobese subjects, the HTGL activity remained significantly higher, by 26%, in Turkish men than in non-Turkish men ($P = 0.008$), and a strong trend ($P = 0.06$) toward higher activity was noted in Turkish women, who

TABLE 4. LpA-I and LpA-I/A-II subfractionation of Turkish subjects' HDL

	Turkish Men (n = 98)	Turkish Women (n = 116)
	mg/dl apoA-I	
LpA-I	32 ± 7	48 ± 10
LpA-I/A-II	75 ± 17	69 ± 16

All values are mean ± SD.

TABLE 5. Spearman correlation coefficients describing the relationship of HTGL and LpA-I with other variables

	Turkish Men		Turkish Women	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
HTGL versus				
HDL-C	0.09[a]	NS	0.247[a]	0.009
LpA-I	0.262[a]	0.01	0.264[a]	0.006
BMI	0.273	0.0077	0.379	0.0001
Triglycerides	0.015	NS	0.384	0.0001
LpA-I versus				
HTGL	0.262[a]	0.01	0.264[a]	0.006
LPL	0.022[a]	NS	0.245	0.01
BMI	0.366[a]	0.0003	0.245[a]	0.01
Triglycerides	0.066[a]	NS	0.305[a]	0.001

[a] Denotes inverse relationship; NS, not significant.

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TABLE 6. Characteristics of nonobese subjects[a]

Characteristic	Men		Women	
	Turks (n = 56)	Non-Turks (n = 23)	Turks (n = 76)	Non-Turks (n = 25)
Age (years)	38 ± 13	34 ± 6	32 ± 10	35 ± 7
BMI (kg/m²)	23.2 ± 2.1	23.4 ± 1.4	21.6 ± 1.8	21.9 ± 2.2
Total cholesterol (mg/dl)	177 ± 47	160 ± 26	172 ± 39	170 ± 28
Triglycerides (mg/dl)	113 ± 44	69 ± 31	77 ± 30	63 ± 13
LDL-C (mg/dl)	116 ± 46	99 ± 28	114 ± 37	97 ± 25
HDL-C (mg/dl)	39 ± 10	47 ± 12	44 ± 9	60 ± 15
Non-HDL-C (mg/dl)	139 ± 50	113 ± 31	128 ± 40	110 ± 24
ApoB (mg/dl)	93 ± 35	94 ± 20	83 ± 27	72 ± 20
ApoA-I (mg/dl)	109 ± 18	134 ± 24	117 ± 24	156 ± 23
CETP (% transfer)	25.3 ± 7.3	28.9 ± 2.4	28.8 ± 8.8	28.2 ± 5.3
LCAT (nmol/ml/h)	241 ± 46	241 ± 31	229 ± 50	289 ± 33
LPL (mmol/ml/h)	11.1 ± 4.4	13.0 ± 4.3	10.1 ± 4.6	13.3 ± 4.9
HTGL (mmol/ml/h)	44.5 ± 14.6	35.3 ± 11.3	32.4 ± 12.2	27.1 ± 8.0
HTGL/LPL	4.4 ± 1.9	3.2 ± 1.6	3.8 ± 2.2	2.3 ± 1.3

All values are mean ± SD.
[a] BMI ≤26 kg/m² for women and ≤25 kg/m² for men.

had 19% higher HTGL activity than non-Turkish women (Tables 6 and 7). Turkish women had slightly lower LPL activities than non-Turkish women ($P = 0.002$), and a similar trend ($P = 0.07$) was noted between the two groups of men. As a result, HTGL/LPL ratios were much higher in Turkish subjects than in non-Turkish controls. The CETP activity was slightly, but significantly, lower in Turkish men than in non-Turkish men. The LCAT activity of the non-Turkish women was significantly greater than that of the other groups.

DISCUSSION

This study confirms the high prevalence of low HDL-C levels in the Turkish population demonstrated in our previous study (17). Turkish men and women had significantly lower HDL-C concentrations than comparable groups of non-Turkish men and women in San Francisco (Tables 1 and 2). This difference persisted even after exclusion of overweight persons from the analysis (Table 6).

TABLE 7. Statistical significance of differences in various characteristics between groups of nonobese subjects[a]

Characteristic	Non-Turkish Men versus Turkish Men	Non-Turkish Women versus Turkish Women
Age	0.39	0.039
BMI	0.74	0.38
Total cholesterol	0.41	0.76
Triglycerides	<0.0001	0.037
LDL-C	0.396	0.041
HDL-C	0.0004	<0.0001
ApoB	0.337	0.024
ApoA-I	<0.0001	<0.0001
CETP	0.009	0.804
LCAT	0.781	<0.0001
LPL	0.071	0.002
HTGL	0.008	0.062
HTGL/LPL	0.0051	0.0003

[a] BMI ≤26 kg/m² for men and ≤25 kg/m² for women.

Multiple factors contribute to low HDL-C concentrations, including obesity, physical inactivity, cigarette smoking, very low fat diets, and various genetic causes. In our previous study of the Turkish population, the first four factors were eliminated as significant causes of low HDL-C levels in Turks, strongly implicating genetic factors (17). Support for a genetic cause also comes from data obtained in Turkish emigrants. For example, Lüttmann et al. (27) reported that Turkish men and women living in Germany had lower mean HDL-C levels than Germans (37 versus 47 mg/dl in men and 46 versus 60 mg/dl for women). Similarly, in a study of Turks living in the San Francisco Bay Area, we found HDL-C levels of 38 ± 9 mg/dl in 64 men (age 42 ± 9 years, BMI 25.7 ± 3.1 kg/m²) and 48 ± 8 mg/dl in 23 women (age 44 ± 7 years, BMI 24.2 ± 2.9 kg/m²) (T. P. Bersot and R. W. Mahley, unpublished data). In contrast, 13 non-Turkish wives (of western European descent) of Turkish men living in San Francisco had HDL-C concentrations of 57 ± 6 mg/dl. Thus, low plasma HDL-C levels are characteristic of Turks living outside of Turkey, a finding that increases the likelihood that low HDL-C levels among Turks are due to a genetic rather than an environmental (e.g., dietary) cause.

Several lipid-related factors are associated with reduced plasma HDL-C concentrations, including elevations in serum triglyceride level and in HTGL and CETP activities and reductions in LPL activity and apoA-I production rate (15, 28–34). The present study was carried out to determine whether the Turkish population has unique alterations in metabolic factors that can account for their low HDL-C concentrations. Identification of these factors would open the door to the study of candidate genes underlying the metabolic aberrations responsible for low HDL-C levels in the Turkish population.

Plasma HDL-C concentrations correlate with BMI (35). Although low HDL-C levels in the Turkish population cannot be explained by obesity, the mean BMI was approximately 1 kg/m² higher in our Turkish subjects than in the non-Turkish controls. However, when nonobese subjects

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were excluded from the analysis, distinct metabolic differences between the two populations persisted (Tables 6 and 7). For example, nonobese Turkish men and women had significantly higher plasma triglyceride levels than their non-Turkish counterparts. Although significant, the differences were small, and total triglyceride levels are generally not elevated in the Turkish population (17) and were not elevated in the study participants (mean <115 mg/dl in all four groups). Analysis of covariance provided further assurance that the higher triglyceride levels in the Turkish subjects did not account for their lower HDL-C levels (Table 3). Adjustment for differences in triglycerides, BMI, and age did not substantially change the differences in HDL-C levels in Turkish and non-Turkish subjects.

The most striking finding in this study was the higher HTGL activity in the Turkish men and women than in non-Turkish controls (Table 1). After exclusion of obese subjects, HTGL activity remained higher in Turkish than in non-Turkish men, and a strong trend ($P = 0.06$) toward higher activity was noted for Turkish women (Table 6). Thus, with respect to factors affecting HDL-C levels, elevated HTGL activity stands out as a distinguishing characteristic between Turkish and non-Turkish groups.

Several lines of evidence have implicated elevated HTGL activity as a cause of low HDL-C. For example, men have consistently higher HTGL activity than women and consistently lower HDL-C levels (36). Also seen in our subjects, this difference is probably due to higher androgen levels in men, as administration of oral androgen preparations to men markedly increases HTGL activity and reduces HDL-C concentrations (37, 38). Obesity is also associated with elevated HTGL and reduced HDL-C levels (39, 40). In the United States, patients with isolated low HDL-C have higher HTGL activity on average than subjects with normal HDL-C levels (24). Finally, African-American men have higher HDL-C levels and lower HTGL activity than white men (41), establishing a precedent for a population-based variation in HTGL activity. Thus, evidence is mounting that HTGL activities are significantly and inversely correlated with plasma HDL-C levels and that this correlation may be causal. Indeed, in the current study, higher HTGL activity was closely associated with low HDL-C levels in Turks, even after exclusion of obese subjects (Tables 6 and 7). Most likely, the higher HTGL activities in this population have a genetic basis.

The genetic basis for differences in HTGL activity has not been determined. A high frequency of a polymorphism in the HTGL gene promoter, which is associated with reduced HTGL activity, has been reported for African-Americans (41). Whether different polymorphisms in the HTGL gene or its control elements exist in Turks remains to be determined. The Turkish population obviously represents an important group for study of genetic factors regulating the expression of HTGL.

It is possible that the genetic basis of elevated HTGL resides in factors regulating the transcription of HTGL that are independent of the gene itself. For example, it has been reported that insulin resistance, independent of obesity, is accompanied by low HDL-C levels (42). Thus, insulin resistance occurring on a genetic basis might lead to high HTGL activity. Whether the Turkish population has a high prevalence of insulin resistance, independent of obesity, remains to be determined. An unusually high prevalence of type 2 diabetes, a characteristic of many insulin-resistant populations, has not been reported in Turkey, but further investigation could be revealing (43). The possibility that Turks have a more generalized metabolic aberration, of which elevated HTGL activity may be but one component, is suggested by the trend toward higher plasma triglyceride levels and lower LPL activity among Turks in the current study. Especially noteworthy were the markedly higher HTGL/LPL ratios in Turks than in non-Turks. Although the biological significance of this ratio is uncertain, it is possible that HTGL and LPL may be metabolically linked, albeit inversely in their expression (44); if so, the marked difference in HTGL/LPL ratios between the two populations could reflect a fundamental metabolic difference between Turks and non-Turk Caucasians. Still, with respect to differences in HTGL activities, at this stage of our investigation it is not possible to differentiate between polymorphism in the HTGL gene and a more generalized metabolic alteration as the genetic basis for elevated HTGL activity in Turks. Additional studies, however, are warranted because the Turkish population appears to be an ideal group for exploring the genetic basis of low HDL-C levels, a common risk factor for coronary heart disease.

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