

# Smoking and obesity make a bad problem worse: genetics and lifestyle affect high density lipoprotein levels in Turks

*Sigara içimi ve obezite ciddi problemi kötüleştireyor: Türk'lerde genetik ve hayat biçimi yüksek dansiteli lipoprotein düzeylerini etkiliyor*

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## ABSTRACT

Low levels of high density lipoprotein cholesterol (HDL-C) are an independent risk factor for coronary heart disease. The Turkish Heart Study revealed very low levels of plasma HDL-C in the Turkish population, a fact confirmed by the Heart Disease and Risk Factors in Turkish Adults study. Low HDL-C levels have also been observed in Turks living in the United States, Germany, and the Netherlands. Dietary habits do not explain the low HDL-C levels, which were found in Turkish Heart Study participants from six regions of Turkey with significant differences in typical diets. Among newborns and pre-pubescent children, plasma HDL-C levels were similar in Turks and western Europeans. After puberty, however, HDL-C levels declined significantly in Turkish boys and girls. These results suggest a genetic basis for the low HDL-C levels. In fact, hepatic lipase activity modulated by sex hormones was 25-30% higher in the Turkish population than in other populations. Elevated hepatic lipase activity is clearly associated with low plasma HDL-C in many studies. Results of a recent genome-wide scan for plasma HDL-C in Turks revealed a linkage on chromosome 15q22 where the hepatic lipase gene is located and that low HDL-C was 80% heritable. In addition, evidence for an interaction between HDL-C levels and modifiable environmental factors, particularly smoking and obesity, came from the study of cholesterol ester transfer protein TaqIB polymorphism. This polymorphism was associated with plasma HDL-C levels in Turks. Subjects with the B2B2 genotype-both smokers and nonsmokers-had higher plasma HDL-C levels. Interestingly, B2B2 subjects were protected from the HDL-C-lowering effect of smoking, whereas B1B1 subjects who smoked had significantly lower HDL-C levels. A similar interaction was observed between TaqIB polymorphism and obesity. In conclusion, low HDL-C levels in Turks were modulated by genetic factors and their interaction with modifiable environmental factors, such as smoking and obesity. (*Anadolu Kardiyol Derg 2006 6: 60-7*)

**Key words:** Smoking, obesity, HDL cholesterol, cholesterol ester transfer protein, Turkish population, polymorphism

## ÖZET

Yüksek yoğunluklu lipoprotein kolesterol (HDL-K) koroner kalp hastalığının bağımsız risk faktörüdür. Türk Kalp Çalışmasında Türk popülasyonunda çok düşük HDL -K seviyeleri saptanmıştır ve bu kanıtlar daha sonra Türk Erişkinlerde Kalp Hastalıkları ve Risk Faktörleri çalışmasında doğrulanmıştır. Düşük HDL-K düzeyleri ABD, Almanya ve Hollanda'da yaşayan Türk'lerde de görülmüştür. Diyet alışkanlıklarında tipik diyetlerde önemli farklılıklar olan, Türkiye'nin altı bölgesinden katılımcılar ile gerçekleştirilen Türk Kalp Çalışmasında, yemek alışkanlıklarının düşük HDL-K seviyelerini açıklamadığı görülmüştür. Plazma HDL-K seviyeleri yeni-doğan ve ergenlik öncesi Türk ve Batı Avrupa çocukları arasında benzer düzeyde bulunmuştur. Ancak, ergenlik çağından sonra, Türk erkek ve kız çocuklarda HDL-K seviyeleri önemli düzeyde düşmektedir.

Bu sonuçlar, HDL-K düzeylerinin bir genetik temele dayalı olduğunu akla getirmektedir. Aslında, seks hormonlarının modülasyonu altında olan hepatik lipaz aktivitesi, Türk popülasyonunda başka popülasyonlara göre %25-30 daha yüksek seviyede olduğu bulunmuştur. Yüksek hepatik lipaz aktivitesinin düşük HDL-K ile ilişkili olduğu birçok çalışmada kanıtlanmıştır. Yakın tarihli, Türk'lerde HDL-K geniş genom taramasında hepatik lipaz geni bulunduran kromosom 15q22 ile bağlantı olduğunu ve HDL-K'nın %80 olarak kalıtsal olduğu gösterilmiştir. Buna ek olarak, kolesterol ester transfer protein TaqIB polimorfizm üzerine yapılan çalışmada, HDL-K ve modifiye edilebilir çevre faktörleri, özellikle sigara içiciliği ve obezite arasında etkileşimler olduğu kanıtlanmıştır. Bu polimorfizm Türk'lerde düşük plazma HDL-K seviyeleri ile ilişkili bulunmuştur. B2B2 genotipli bireylerde - sigara içenlerde ve içmeyenlerde- daha yüksek HDL-K seviyeleri bulunmuştur. İlginç olan, B2B2 bireylerde sigara içiminin HDL-K düşürücü etkisinden korunmuş olduğu gösterilmiştir. Benzer etkileşim, TaqIB polimorfizm ve obezite arasında gözlenmiştir. Sonuç olarak, Türk'lerde düşük HDL-K seviyeleri genetik faktörlerin, bu faktörlerin modifiye edilebilen sigara içiciliği ve obezite gibi çevre faktörlerinin etkileşimlerinin modülasyonu altındadır. (*Anadolu Kardiyol Derg 2006 6: 60-7*)

**Anahtar kelimeler:** Sigara içimi, obezite, HDL kolesterol, kolesterol ester transfer protein, Türk popülasyonu, polimorfizm

## Introduction

Plasma lipid abnormalities, smoking, and obesity are major risk factors for coronary heart disease (CHD), the major cause of death worldwide (1, 2). Coronary heart disease risk is increased by high levels of total cholesterol and low density lipoprotein cholesterol (LDL-C), low levels of high density lipoprotein cholesterol (HDL-C), and high levels of triglycerides (3-8). Plasma lipid levels are regulated by a combination of genetic and environmental factors, including smoking. In a meta-analysis of over 50 published studies, smoking reduced plasma HDL-C levels in a dose-dependent manner. For example, heavy smokers have, on average, 9% lower HDL-C levels than matched nonsmokers (9). Obesity has become a worldwide epidemic, resulting in altered lipid levels and a predisposition to diabetes (10-12).

## Turks Have Very Low HDL-C Levels

The Turkish Heart Study (THS) surveyed approximately 9000 men and women from six regions of Turkey with different dietary habits (13). Notably, the Turkish people were found to have low levels of HDL-C (mean values for all six regions: men, 34-38 mg/dl; women, 37-45 mg/dl), typically 10-15 mg/dl lower than in Europeans and North Americans. Recent THS reports confirm the occurrence of low HDL-C (14). Similar findings were reported by the Heart Disease and Risk Factors in Turkish Adults (TEKHARF) study (15) and in follow-up studies (16, 17). Tezcan et al. reported virtually identical low HDL-C levels in a population in Ankara (18).

Low HDL-C levels in Turks appear to have a major genetic component. Turks living in Germany (19-21), the Netherlands (22), and the United States (23) have low plasma HDL-C levels. Observational studies in the United States have demonstrated that CHD risk increases by 2-4% for every 1 mg/dl decrease in HDL-C levels (8). A similar increase in CHD risk was also observed in the Helsinki Heart Study (24).

Low HDL-C levels are associated with the high cardiovascular morbidity and mortality observed in the Turkish population (17, 25). In fact, a decrease of 12 mg/dl in HDL-C independent of other known risk factors was associated with a 36% increase in nonfatal and fatal CHD events (17, 25). This magnitude of risk is similar to that in other populations (8, 24).

## Smoking Is an Important Health Problem for Turks

Smoking is a major risk factor for CHD. The detrimental effects of smoking include direct effects of the harmful components of smoke on the arterial wall and effects on plasma lipids and lipoproteins. Smoking has been associated with a variety of unfavorable effects on specific lipoprotein levels, such as low plasma HDL-C levels (26-28). Smoking may also influence lifestyle choices, such as diet or physical activity, that may contribute to further risk for CHD (26, 29).

The incidence of acute CHD events is two- to sixfold higher in smokers than nonsmokers in Western populations (28, 30). However, smoking itself may not be sufficient to cause a high incidence of CHD in a population. Asian countries, such as Japan, have low CHD rates in spite of higher smoking incidence (26, 31), suggesting that additional genetic and/or environmental factors or their interactions affect CHD outcome.

Smoking is very common among Turks; over half of the men (58%) and over one quarter of the women (29%) smoke one or more cigarettes a day (13). The TEKHAHF study also found a similar smoking prevalence in 1990: 60% of males and 19% of females (32). In the 1970s, prevalence of smoking began to diminish in both genders, with a profound decline in males in Western societies (33). However, in Turkey, from 1970 to 1998, per capita cigarette consumption gradually increased by about 20% (34). Compared to 1990 data, the year 2000 cohort of the TEKHAHF study found smoking prevalence was reduced 18% in males and increased 24% in females in middle-age or older groups (35). To evaluate population trends for smoking, the original THS 1990-1993 results for Istanbul region were compared with the 1996-2000 and 2003 data from Istanbul (14). Overall, the incidence of smoking decreased slightly from 1990-1993 to 2003 (14), but it was associated with educational level. At all three time points, the prevalence of smoking was greater in lower education groups than higher education groups (39-57% vs 37-41% in males; 29-44% vs 24-38% in females, respectively). In a recent, large cross-sectional study (TURDEP), the prevalence of smoking was 51% for adult Turkish males and 11% for adult Turkish females (36). Thus, the THS, TEKHAHF, and TURDEP studies all agree that smoking is still a major health issue for Turkey. Although smoking is associated with low HDL-C, smoking does not account for the markedly low levels of HDL-C in Turks (13-15). As shown in Table 1, there was a 1.3 mg/dl lower HDL-C in males who smoked, but no difference in females was observed between smokers and nonsmokers.

## Obesity and CHD Risk in Turks

Obesity is an independent risk factor for a number of life-threatening and debilitating conditions, including CHD, type 2 diabetes mellitus, and certain types of cancers (10-12). The prevalence of obesity is increasing at an alarming rate in many parts of the world (10-12). In the 1990 cohort of the TEKHAHF study for those age 30 and over, the prevalence of obesity [body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>] was 12% in males and 32% in females (37). A decade later, the TEKHAHF 2001/2002 cohort revealed a striking increase to 25% in males and 44% in females (38). In the original THS (1990-1993), obesity prevalence for age  $\geq 30$  was similar to that of the TEKHAHF study: 13% in males and 24% in females (13), and mean BMI and obesity prevalence gradually increased in the 1996-2000 and 2003 cohorts of both genders (14). Education levels were shown to play a role in the prevalence of obesity. A higher level of education was associated with a lower prevalence of obesity (low vs high education in 2003: males, 34% vs 26%; females, 45% vs 15%) (14).

Body mass index correlates with systolic and diastolic blood pressures, plasma triglyceride levels, and total cholesterol/HDL-C ratio and inversely with plasma HDL-C levels (13, 39, 40). The TEKHAHF study revealed that BMI ( $\geq 30$  kg/m<sup>2</sup>) was associated with CHD in women in both the 1990 (odds ratio of 1.76) and 1998 surveys (each kg/m<sup>2</sup> of BMI increased CHD risk by 11%). It was also an independent predictor in men for coronary events and death, conferring 10% additional risk for every kg/m<sup>2</sup> of BMI (17).

## Genetic Variants of the Cholesterol Ester Transfer Protein

High density lipoprotein mediates the transport of cholesterol from the periphery (including the arterial wall) to the liver

where it is secreted. This process, called reverse cholesterol transport, generally refers to the atheroprotective effect of HDL. Cholesterol ester transfer protein (CETP), a protein in the reverse cholesterol transport pathway, is mainly associated with HDL particles in the circulation (41, 42). Cholesterol ester transfer protein promotes the transfer of cholesteryl esters from HDL to apolipoprotein B-containing particles (very low density lipoproteins and LDL) in exchange for triglycerides (Figure 1) (43). Because it participates in reverse cholesterol transport, CETP is considered antiatherogenic. However, it also increases LDL-C and decreases HDL-C levels, suggesting that it is atherogenic. A complicated balance of several lipoprotein genes, diet, and other environmental factors likely modulates the net effect of CETP on the arterial wall (44), but control of CETP activity is a tempting therapeutic strategy.

Recent human trials with CETP inhibitors (45, 46) showed significantly increased HDL-C and decreased LDL-C levels, suggesting antiatherogenic benefits of inhibiting CETP activity. Although CETP deficiency might be atherogenic (47), partial inhibition of CETP may not result in an atherogenic lipid profile (48); residual CETP activity may prevent the accumulation of very large abnormal HDL and LDL particles (46).

Several polymorphisms have been identified in CETP. The most studied is TaqIB, a silent base change in the first intron. While the rare B2 allele is associated with increased HDL-C levels and decreased CETP levels, the common B1 allele is associated with decreased HDL-C levels and increased CETP activity. This association between TaqIB and HDL-C has been observed in most (49-53) but not all populations examined (54, 55).

The TaqIB polymorphism is in strong linkage disequilibrium with - 629C>A (56), and - 629A displays lower transcriptional activity in vitro than - 629C (57). Thus, the TaqIB polymorphism may be a marker for the - 629C>A promoter polymorphism.

### CETP TaqIB Polymorphism and HDL-C in Turks

To determine the frequency of the TaqIB polymorphism in the Turkish population, over 2000 random DNA samples were genotyped (58). The frequency of the B2 allele was 44%, similar to that found in other populations (49-55). Plasma HDL-C levels were 8-9% lower in Turkish men and women with the B1B1 genotype than in those with the B2B2 genotype (Table 2). Stratification of HDL-C levels by genotype and allele revealed that the frequency of low HDL-C was significantly higher in individuals with the B1B1 genotype and the B1 allele, whereas high HDL-C levels were associated with the B2B2 genotype and the B2 allele (58). These results are consistent with those reported in a small cohort of Turks by Yilmaz et al. (59). Healthy subjects and CHD patients with the B1B1 genotype had lower HDL-C levels than those with B2B2 (59). No other associations with lipid parameters (triglyceride, total cholesterol, LDL-C, and total cholesterol/HDL-C ratio) were found (Table 2).

As noted above, both genetic and environmental/lifestyle factors interact to modulate HDL-C levels. Cholesterol ester transfer protein TaqIB genotype and activity were examined in the context of smoking and BMI.

Smoking and HDL-C. The interaction of smoking and the CETP TaqIB polymorphism on HDL-C has been examined in se-

**Table 1. Interaction between cholesterol ester transfer protein TaqIB polymorphism and smoking and obesity on HDL-C levels (mg/dl ± SD) in Turks**

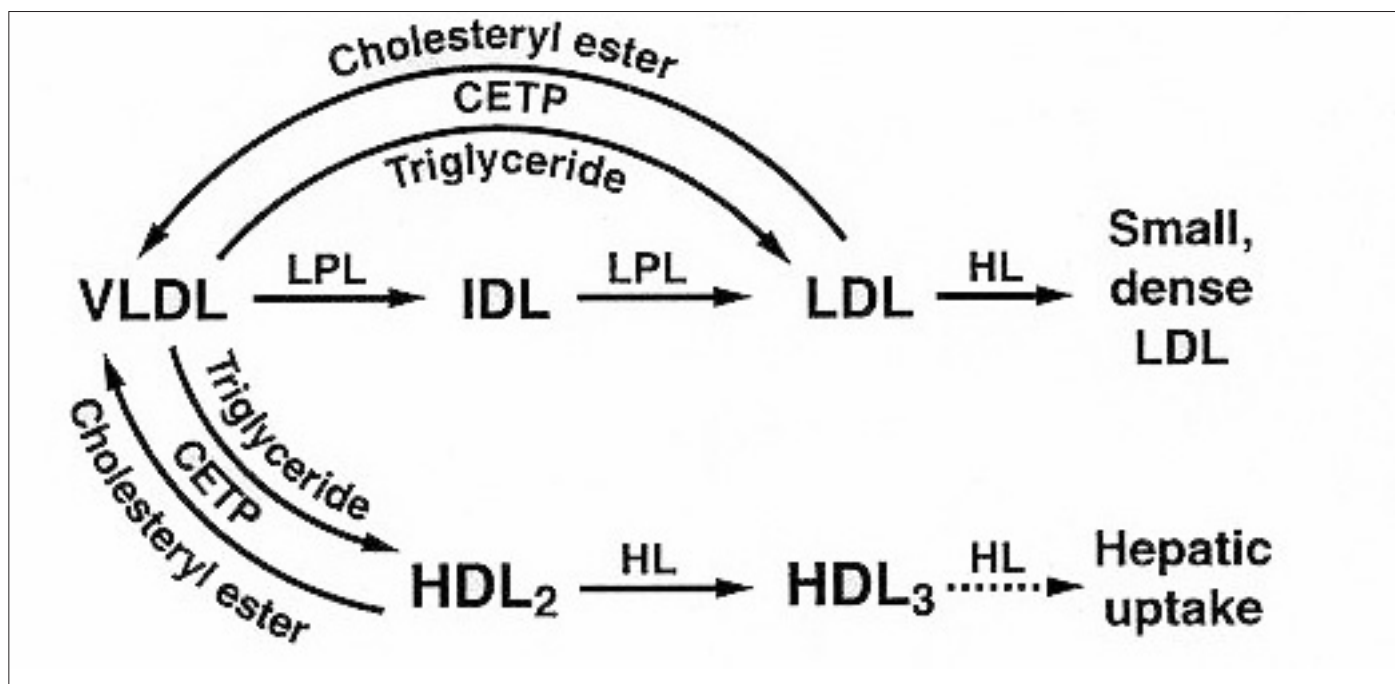
	All	B1B1	B1B2	B2B2	P B1B1 vs B2B2	% Increase in HDL-C B2B2 vs B1B1
<b>Males</b>						
Smoking, cigarettes/day						
0	36.2 ± 6.6 (509)	35.1 ± 5.7 (162)	35.8 ± 6.8 (241)	37.1 ± 6.9 (106)	<0.05	5.7
1-19	34.9 ± 6.2 (335)	34.0 ± 4.6 (101)	34.5 ± 6.5 (173)	37.5 ± 7.1 (61)	<0.001	10.3
20+	34.9 ± 6.7 (375)	32.8 ± 5.5 (116)	34.5 ± 6.1 (180)	37.0 ± 8.7 (79)	<0.001	12.8
P (0 vs. 20+)	0.01	0.005	NS	NS		
BMI, percentile						
<50th	36.2 ± 6.5 (592)	35.3 ± 5.7 (183)	36.1 ± 6.7 (284)	37.9 ± 6.8 (125)	<0.005	7.3
≥50th	34.2 ± 6.4 (595)	32.9 ± 4.9 (187)	34.2 ± 6.3 (290)	36.4 ± 8.1 (118)	<0.001	10.5
P (<50th vs. ≥50th)	<0.001	<0.001	<0.001	NS		
<b>Females</b>						
Smoking, cigarettes/day						
0	40.9 ± 7.8 (559)	40.2 ± 7.3 (180)	40.8 ± 7.8 (268)	42.3 ± 8.5 (111)	<0.05	5.2
1-19	41.2 ± 8.2 (168)	40.3 ± 8.2 (48)	40.9 ± 7.3 (90)	43.4 ± 10.2 (30)	<0.05	7.7
20+	40.9 ± 9.8 (65)	35.5 ± 4.0 (19)	41.3 ± 7.4 (32)	43.6 ± 10.2 (14)	<0.05	23.2
P (0 vs. 20+)	NS	<0.005	NS	NS		
BMI, percentile						
<50th	42.7 ± 8.7 (390)	41.9 ± 7.8 (119)	42.8 ± 8.3 (195)	43.7 ± 11.0 (76)	NS	4.2
≥50th	39.2 ± 6.9 (390)	37.8 ± 6.5 (124)	38.9 ± 6.4 (190)	42.1 ± 8.0 (76)	<0.001	11.2
P (<50th vs. ≥50th)	<0.001	<0.001	<0.001	NS		

Values in parentheses are numbers of subjects. P values were determined by t test. BMI - body mass index, HDL-C - high density lipoprotein cholesterol, NS - not significant

veral studies with mixed results. Some groups (60-62) have seen an association between TaqIB genotype and plasma HDL-C levels only in smokers, while others have seen it in both smokers and nonsmokers (63, 64). Additionally, the TaqIB B2 allele has been associated with reduced risk of CHD (51, 65-67), but only in nonsmokers (65).

In a study with a much larger population base, we found a clear association (58). In male and female smokers and nonsmokers with the B1B1 genotype, HDL-C levels were signifi-

cantly lower than those with the B2B2 genotype. However, in those with the B1B1 genotype, smoking was associated with a marked reduction in HDL-C levels (Table 1), whereas the B2B2 genotype appears to protect against the HDL-C-lowering effect of smoking. High density lipoprotein cholesterol levels were lower in smokers (males: 7%; females: 13%) than nonsmokers with the B1B1 genotype. In fact, in heavy smokers (>20 cigarettes/day) with the B1B1 genotype, the HDL-C levels were 13% and 23% lower in men and women, respectively, than in



**Figure 1.** Cholesterol ester transfer protein (CETP) and hepatic lipase (HL) are key regulators of high density lipoprotein cholesterol (HDL-C). The CETP transfers cholesteryl esters from HDL2 to triglyceride-rich lipoproteins in exchange for triglyceride going to HDL to make HDL2. Triglycerides in the HDL2 are substrates for HL, which hydrolyzes the triglycerides to convert HDL2 to HDL3. HL is also involved in the uptake of cholesterol from HDL by the liver. In addition, HL converts triglyceride-rich LDL particles to small, dense LDL. High levels of HL result in a reduction of HDL, especially the atheroprotective HDL2, and increase atherogenic small dense LDL.

IDL- intermediate density lipoproteins, LPL- lipoprotein lipase, VLDL- very low density lipoproteins

**Table 2.** Cholesterol ester transfer protein TaqIB polymorphism and plasma lipid levels (mg/dl) (Mean ± SD) in Turks

	All	B1B1	B1B2	B2B2	P B1B1 vs B2B2
<b>Males</b>					
Triglycerides	151 ± 113 (1221)	155 ± 111 (379)	147 ± 99 (595)	152 ± 142 (247)	NS
Total cholesterol	198 ± 151 (1221)	197 ± 151 (379)	202 ± 176 (595)	191 ± 46 (247)	NS
LDL-C	131 ± 112 (1186)	133 ± 151 (366)	132 ± 103 (578)	125 ± 41 (242)	NS
HDL-C	35.2 ± 6.5 (1219)	34.1 ± 5.5 (379)	35.0 ± 6.6 (594)	37.2 ± 7.5 (246)	<0.001
TC/HDL-C ratio	5.7 ± 3.2 (1218)	5.9 ± 4.1 (379)	5.7 ± 3.0 (593)	5.3 ± 1.8 (246)	NS
<b>Females</b>					
Triglycerides	117 ± 107 (791)	121 ± 138 (247)	113 ± 82 (390)	120 ± 103 (154)	NS
Total cholesterol	184 ± 48 (792)	181 ± 45 (246)	184 ± 51 (393)	190 ± 47 (153)	NS
HDL-C	41.0 ± 8.2 (792)	39.9 ± 7.4 (247)	40.9 ± 7.7 (390)	43.0 ± 9.6 (155)	<0.001
LDL-C	120 ± 41 (777)	118 ± 38 (241)	120 ± 44 (386)	125 ± 37 (150)	NS
TC/HDL-C ratio	4.7 ± 1.5 (792)	4.7 ± 1.6 (247)	4.6 ± 1.5 (390)	4.7 ± 1.5 (155)	NS

Values in parentheses are numbers of subjects. P values were determined by t test. HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, NS- not significant, TC- total cholesterol

those with the B2B2 genotype.

It is difficult to reach a conclusion about whether smoking affects plasma CETP activity. Activities have been reported as higher (68, 69) or lower (70, 71) in smokers than in nonsmokers. Several conditions, such as population-specific characteristics of study samples, environmental factors, selection criteria, and sample size, may contribute to the inconsistencies. We (58) and others (72, 73) saw no differences in plasma CETP activities between smokers and nonsmokers. However, we found that smokers with the B2B2 genotype had significantly lower CETP activity. Thus, we suggested that the TaqIB genotype interacts with smoking to affect CETP activity and consequently plasma HDL-C levels (58). The lower levels of CETP activity in B2B2 subjects may be beneficial, causing HDL-C levels to remain high even under conditions that might otherwise lower HDL-C levels. For example, lower CETP levels may protect against the HDL-C-lowering effects of smoking. On the other hand, in B1B1 subjects who have higher levels of CETP activity, HDL-C levels may be more susceptible to the reducing effects of smoking. Smoking is prevalent among Turks (13, 32, 34-36), and part of the low HDL-C levels in Turks may result from the interaction between CETP and smoking.

**Obesity and HDL-C.** An understanding of this relationship is particularly important for a population with low plasma HDL-C levels and increasing obesity trends. Cholesterol ester transfer protein activity did not differ between the BMI <50th and ≥50th percentile groups in Turks (58). However, in a small study group, CETP activity increased with obesity (74).

In our large-scale study (58), we stratified subjects by their TaqIB genotypes and BMI values (Table 1). High density lipoprotein cholesterol levels were significantly lower in males and females with BMI ≥50th percentile. The TaqIB association with HDL-C levels was not affected by high or low BMI, and in individuals from both BMI groups, those with B1B1 had significantly lower HDL-C levels than those with B2B2. However, BMI and TaqIB genotype did interact to influence HDL-C levels. No difference was observed between high and low BMI in B2B2 subjects, whereas clear differences were observed in B1B1 subjects on plasma HDL-C levels (Table 1). Thus, the B2B2 genotype appears to protect against HDL-C lowering associated with obesity.

### **Hepatic Lipase Genetic Variants and Effects on Plasma HDL-C Levels**

Hepatic lipase (HL) is one logical candidate for involvement in the low Turkish HDL-C levels. With its triglyceride hydrolase and phospholipase activities, HL is an important modulator of HDL metabolism (Figure 1). Higher HL activity and mass are correlated with low plasma HDL-C levels (75). Turks have a 25-30% increase in HL activity and mass (23, 76).

Plasma HDL-C levels at birth and pre-puberty are very similar among Turks, Americans and Europeans, and almost identical between boys and girls (77-79). After puberty, HDL-C levels in western European males and females decrease to typical adult levels. However, HDL-C levels in Turkish boys drop strikingly from a mean of 58 to 37 mg/dl and in Turkish girls from 55 to 43 mg/dl and remain at similarly low levels in adulthood (13, 15).

The mechanism for this remarkable reduction in HDL-C levels is unknown. Obviously, sex steroids are always suspect during puberty, and it has been suggested that Turks have lower levels of sex hormone-binding globulin that may result in

increased levels of free bioactive testosterone in both males and females (20). Production of HL is regulated by androgens, and increased mass and activity of HL are associated with increased levels of androgens (80). However, numerous factors change at puberty, including plasma levels of leptin, adiponectin, and insulin, and may contribute to the high levels of HL mass and activity associated with very low plasma HDL-C levels that are characteristic of Turkish populations.

Elevated HL activity and reduced HDL-C levels are also associated with obesity (81). However, although obesity is prevalent among Turks, it may not explain high HL activity, because elevated HL levels were observed in normotriglyceridemic and nonobese in this population (23).

Additional insights into the low levels of HDL among Turks have recently come from the Genetic Epidemiology of Metabolic Syndrome study. This is a large, international and family-based study designed to explore the genetic basis of atherogenic dyslipidemia. This study has examined families from six different countries, including Turkey (82). Results showed that serum lipid levels were significantly influenced by genetics. As noted, heritability estimates for HDL-C were much higher for the Turkish group than other groups (50-60% for populations of western European ethnicity vs 80% for Turks) (82). The most significant linkage finding for HDL-C was on chromosome 15q22 (logarithm of the odds ratio, LOD = 3.05) in the Turkish families. The HL gene is located in 15q21-15q23 (82) and may account for the linkage peak in this region (83).

Association studies with variants of the HL gene, especially with promoter polymorphisms, have also been conducted. The four promoter polymorphisms (-250G>A, -514C>T, -710T>C, and -763A>G) were in complete linkage disequilibrium (83) as in the Turks (unpublished data). The promoter polymorphism -514C>T was associated with HL activity. Subjects with the -514CC genotype had a higher HL activity than those with the -514TT genotype in Turks (76). A recent meta-analysis for the -514C>T polymorphism showed significant decreases for HL activity and increases for plasma HDL-C levels for both the CT and TT genotypes compared with the CC genotype (84). In vitro studies suggested that the -514C>T variant was functional (85).

Thus, as a candidate gene to explain the low HDL levels in Turks, HL is supported by several lines of evidence, including the association of high HL activity and mass with low plasma HDL-C levels (23), increased free testosterone levels that may increase HL activity (20), genome scans demonstrating linkage at the 15q22 locus where HL is located (82), and the association with the -514C>T polymorphism (76, 86). Many areas are currently under investigation, including common polymorphisms and haplotypes and their association with plasma HDL-C levels and HL activity, as well as potential genetic/lifestyle factors interacting to modulate plasma HDL-C levels in Turks.

### **Conclusion**

Recent developments in molecular biology and genetics have suggested that almost all human diseases are complex and our genes make a necessary and major, but only partial, contribution. Environmental factors and their interactions with the genetic background during the life of an individual may also be important to manifest or modulate the magnitude of the disease or any given phenotype.

The low plasma HDL-C levels among Turks are an excellent example. Environmental factors and lifestyle choices, such as smoking and obesity, are clearly involved. Genetics also plays a role. Common polymorphisms and/or haplotypes of CETP (58), HL (76), ATP binding cassette transporter A1 (87), apolipoprotein A5, (88) and acyl-CoA:diacylglycerol acyltransferase (89) genes are important modulators of plasma HDL-C and triglyceride levels in Turks. Although the CHD risk conveyed by any polymorphism may be small, the risk from multiple polymorphisms could be significant.

Fortunately, complex diseases do not always require complex treatments. Simple strategies may yield large benefits. In fact, modifiable behavioral factors, including specific aspects of diet, body weight, physical activity, and smoking, accounted for over 80% of CHD (90). Understanding the interactions of genetics and environmental factors can help to focus the public health effort needed to change these patterns in the Turkish population.

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