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DERLEMELER

Low Levels of High-Density Lipoproteins in the Turkish Population: A Risk Factor for Coronary Heart Disease

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TÜRKLERDE DÜŞÜKLÜĞÜ YÜKSEK DANSİTELİ LİPOPROTEİN: KORONER KALP HASTALIĞI İÇİN BİR RİSK FAKTÖRÜ

ÖZET

Yüksek dansiteli lipoprotein kolesterole (HDL-K) ilişkin düşük düzeyler Türklerde diğer incelenmiş popülasyonlara kıyasla daha sıktır. Bu düşük HDL-K düzeyleri besin yağı tüketimiyle ilgili bölgesel farklara bağlı olmayarak görülmektedir. Türk erkeklerinin yaklaşık %50'si ve kadınlarının %25'i <35 mg/dl gibi istenmeyen ölçüde düşük HDL-K düzeylerine sahiptir. Hepatik lipaz aktivitesi (muhtemelen genetik kökenli ve Amerikalı kontrollere kıyasla %25-30 daha yüksek düzeyler) bu yaygın düşük HDL-K'ü açıklar görünmektedir. Hepatik lipazın yüksekliği ile birlikte, sigara içimi, fizik inaktivite, şişmanlık ve trigliserid düzeylerini yükselten diyetler gibi sekonder çevresel ve metabolik etkenler HDL-K'ü daha fazla düşürebilir. Birçok Türk'ün total kolesterol düzeyleri düşük olmakla beraber, çok düşük HDL-K seviyeleri total kolesterol/HDL-K oranını tehlikeli bir ölçüde yükseltir. "Normal" sayılan 200 mg/dl'lik total kolesterol seviyesi dahi, 35 mg/dl'lik HDL-K düzeyi eşliğinde 5.7'lik bir orana yol açar. İncelemelerde bu oranın yüksek bir koroner kalp hastalığı riskiyle birlikte gittiği göze çarpmaktadır. Böylece, düşük HDL-K çerçevesinde normal kolesterol düzeyinin ne olduğunun tanımlanması gerekmektedir. Yeni klinik denemelerden sağlanan veriler düşük HDL-K'lü hastaları tedavi etmenin ve total kolesterol/HDL-K oranını azaltmanın kalp hastalığının hem primer, hem sekonder önlenmesinde yararlı olduğunu göstermektedir.

Anahtar Kelimeler: Koroner kalp hastalığı riski, lipoproteinler, plazma lipidleri, Türk popülasyonu

Over the years, population studies have provided unique insights into the importance of specific lipoproteins in causing premature coronary heart disease (CHD) [1-4]. This is especially true when we look at the lipid levels and lipoprotein profiles of the Turkish people. Because of unique differences in the Turks compared with other populations, we must reconsider diagnostic and treatment approaches in the context of the low high-density lipoprotein cholesterol (HDL-C) levels that are so prevalent in Turkey.

In the United States, it has been established that it is desirable to have a total plasma cholesterol of <200 mg/dl and that there is definitely an increase in risk at levels >240 mg/dl [1-4]. HDL-C levels should be >35 mg/dl, and preferably >45 mg/dl. The risk of heart disease increases markedly when HDL-C values are below 35 mg/dl [5-8]. The detrimental effects of high cholesterol and low HDL-C levels are reflected in the total plasma cholesterol to HDL-C ratio. The optimal ratio is <3.5, and data from the Framingham Study indicate that a ratio >4.5 is associated with increased risk [9-11]. These guidelines and cut off points were established in the United States and Europe on the basis of populations with average HDL-C levels of ~47 and ~60 mg/dl for men and women, respectively. However, in Turkey, average HDL-C levels are 10-15 mg/dl lower (mean: 37 mg/dl in men and 43 mg/dl in women) [12]. Here, we will review the key results documenting the unique features of the Turkish lipoprotein profile, we will suggest possible molecular and genetic mechanisms responsible for these observations, and we will consider important aspects in the treatment of patients with the Turkish lipid profile.

TURKISH HEART STUDY AND THE UNIQUE LIPID PROFILE OF TURKS

The Turkish Heart Study, which began around 1990, was designed to survey approximately 9,000 volunteer Turkish participants in cities, towns, and villages throughout Turkey [12]. Each participant provided a detailed personal, social, and medical history with which to assess risk factors for cardiovascular

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disease and a blood sample for plasma lipid and lipoprotein analyses. All lipid determinations were performed in the Clinical Laboratory at the Koç American Hospital in Istanbul (a certified reference laboratory directed by Dr. K. Erhan Palaoğlu).

Six regions were selected on the basis of differences in lifestyle, especially differences in dietary fat consumption. Istanbul was selected because it is a large metropolitan urban center. The Adana, Trabzon, and Kayseri regions were chosen because their diets tend to be high in saturated fats. Aydın was selected because its diet is high in polyunsaturated fats, and Ayvalık because of a diet rich in monounsaturated fats (olive oil). The dietary differences were confirmed by the analysis of blood cholesteryl ester fatty acids, which established the general impressions concerning dietary differences [12].

The plasma cholesterol levels were different in the various regions (Table 1). The highest levels were seen in the Istanbul men -a mean of ~202 mg/dl - which is very similar to the mean seen in the United States and Europe (populations known to be at high risk for CHD). The next highest levels -170-190 mg/dl- were seen in the men and women in Adana, Trabzon, and Kayseri areas of the country where the consumption of saturated fat is highest. The lowest mean levels, about 160 mg/dl, were seen in the Ayvalık population, where monounsaturated fats are common in the diet. These results are similar to those obtained by Onat et al. [13] and the Turkish Society of Cardiology.

Consistent with conclusions drawn by Onat et al. [13], Turks have rather low mean plasma cholesterol levels. In the Turkish Heart Study, about two-thirds of the men and three-fourths of the women had levels <200 mg/dl. Despite these generalized low plasma cholesterol levels, there was clearly a segment of the Turkish population that was at high risk. About 20% of the Turkish men in the Istanbul sample had cholesterol levels >240 mg/dl. This is similar to the proportion of U.S. men who have such undesirably high cholesterol levels. In contrast, only 3-6% of the men and women in Aydın and Ayvalık had cholesterol levels >240 mg/dl. Strikingly, Ayvalık men and women had mean plasma cholesterol and low-density lipoprotein cholesterol (LDL-C) levels of ~160 and ~90 mg/dl, respectively (some of the lowest levels in the world) (Table 1) [12].

It was clearly established that the most affluent, most highly educated men and women had the highest cholesterol levels (30-40 mg/dl higher in subjects with the highest salaries than in those with the lowest salaries). The availability of high-calorie, high-fat foods was associated with marked elevations of cholesterol and LDL-C levels in the Turkish population [12]. Therefore, high cholesterol levels are a problem in a subset of the Turkish population, and levels are as high as those seen in Western populations, which are known to be at high risk for CHD.

One of the most important findings of the Turkish Heart Study was the great prevalence of low levels of HDL-C in the Turkish population (Table 1) [12]. Turkish men had HDL-C of 34-38 mg/dl, which is at least 10 mg/dl lower than HDL-C in American or European men. Turkish women had HDL-C levels of 37-45 mg/dl, which are 10-15 mg/dl lower than those seen in American or European women. These observations have been confirmed and extended by Onat et al. [14]. These HDL-C levels are among the

Table 1. Age-adjusted plasma lipid levels of men and women in various regions of Turkey*

	Total Cholesterol		LDL-C		HDL-C		Cholesterol/ HDL-C Ratio		Triglycerides	
Location	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Istanbul	202	181	136	117	38	45	5.5	4.2	142	90
Adana	184	190	121	129	34	39	5.6	5.1	145	109
Trabzon	174	175	115	115	34	42	5.3	4.3	129	95
Kayseri	171	179	111	119	34	37	5.1	5.0	128	121
Aydın	173	166	107	103	37	43	4.8	4.0	143	95
Ayvalık	160	162	100	99	38	42	4.3	3.9	124	112
n	6085	2932	5943	2908	6085	2932	6085	2932	6085	2932

**Mean mg/dl; modified from reference 12*

lowest of any population in the world, and they may represent an important risk factor in the Turkish population. Another important point to note is that the HDL-C levels were low throughout Turkey, regardless of the major differences in diet. This and other results suggest that the low HDL-C may primarily have a genetic cause.

To rule out environmental and lifestyle factors as being responsible for the generalized low HDL-C in Turks, we studied Turks living abroad, many of whom undoubtedly had adopted non-Turkish lifestyles. As shown in Table 2, Turkish men living in Germany had a mean HDL-C level of 38 mg/dl, which is essentially identical to those of Turks living in Turkey but very different from those of Germans or Americans [15]. Likewise, Turkish women living in Germany had low HDL-C levels similar to those of Turkish women in Turkey but approximately 10-15 mg/dl lower than those of German or American women. Furthermore, Turks living in San Francisco had low HDL-C levels essentially identical to those of Turks living in Germany or Turkey.

Thus, HDL-C is abnormally low in the Turkish population. About 50% of Turkish men, but only 15% of U.S. men, have HDL-C <35 mg/dl. About 25% of Turkish women, but only 5% of U.S. women, have HDL-C <35 mg/dl. This major ethnic difference in HDL-C levels could become even more of a major CHD risk factor as LDL levels undoubtedly will tend to rise as Turkey becomes more developed and industrialized. As socioeconomic status improves, individuals consume diets higher in saturated fat, a factor that increases LDL levels [12].

Based on the finding of generalized low HDL-C in Turks living in six different regions of Turkey, where the diets differ significantly, as well as in Turks living in Germany and the U.S., we have hypothesized that the low HDL-C is primarily genetic in origin. In addition, several environmental or metabolic factors can contribute to lowering HDL-C [16-18]. These include smoking, lack of physical activity, obesity, and diets that raise triglyceride levels -all of these factors are prevalent in Turkey. Therefore, the genetically low HDL-C could be made even worse by these environmental factors. However, all our data indicate that none of these secondary factors are the major cause of the low HDL-C.

HDL METABOLISM AND HEPATIC LIPASE

High-density lipoproteins serve as acceptors for excess cholesterol from cells and participate in the transport of cholesterol from peripheral tissues to the liver for excretion from the body (for review, see ref. 19). Therefore, high levels of HDL are considered to be desirable, presumably because they facilitate the transport of cholesterol out of the artery wall. On the other hand, low HDL-C is a risk factor for premature CHD.

As illustrated in Figure 1, various enzymes and transfer proteins are involved in HDL metabolism, and their activities control the levels of HDL in the plasma (for review, see ref. 19). Precursors of HDL are of several origins, including excess surface material shed from chylomicrons and very low-density lipoproteins (VLDL) during lipolysis, and are disks composed primarily of apolipoprotein AI, phospholipid, and free cholesterol (pre-HDL).

As additional cholesterol is acquired by the pre-HDL, the cholesterol is esterified by the activity of

Table 2. Comparison of plasma lipids among different populations*

	Americans (in the U.S.)		Germans (in Germany)**		Turks (in Germany)		Turks (in Istanbul)		Turks (in Ayvalık)		Turks (in San Francisco)***	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Total Cholesterol	206	208	218	211	193	174	202	181	160	162	220	213
HDL-C	47	56	47	60	38	46	38	45	38	42	38	46
Total Cholesterol/ HDL-C ratio	4.5	3.8	4.6	3.5	5.1	3.8	5.5	4.2	4.3	3.9	5.8	4.6

**Mean mg/dl; modified from reference 12; see original report for details.*
***See reference 15.*
****Unpublished data from 39 Turkish men and 15 Turkish women residing in San Francisco.*

lecithin:cholesterol acyltransferase. The newly synthesized cholesteryl esters form the core of the smallest HDL (HDL_3), and a spherical particle is produced. Likewise, the HDL_3 may acquire free cholesterol that is esterified, converting these small particles to the larger HDL_2.

Some of the cholesteryl esters of the HDL_2 are transferred to lower density lipoproteins (VLDL and LDL) by the action of the cholesterol ester transfer protein (CETP). In exchange for the cholesteryl esters, CETP transfers triglycerides from the lower density lipoproteins to the HDL_2. Thus, indirectly HDL deliver their cholesterol to the liver, after the esters are transferred to the lower density lipoproteins that are taken up by the liver.

Hepatic lipase possesses both triglyceride hydrolytic and phospholipase activities, plays a significant role in remodeling HDL, and has a major effect on HDL levels (Fig. 1) [19-25]. Primarily located in the liver sinusoids and the space of Disse, hepatic lipase acts on HDL_2 to hydrolyze the excess triglyceride transferred to these particles by CETP and to hydrolyze excess phospholipids to generate the smaller HDL_3. The regenerated HDL_3 can again participate in acquiring cholesterol from cells or tissues with excess cholesterol.

Thus, high levels of some of these factors cause low HDL-C, whereas low levels of other factors cause low HDL-C (Fig. 1). Analysis of the activities of these enzymes and transfer proteins in Turkish subjects revealed that the most striking difference was a 25-30% increase in hepatic lipase activity [26]. High levels of hepatic lipase cause low HDL-C and especially low HDL_2 [8,20]. That is exactly what we find in the Turkish population -low HDL_2 levels, decreased HDL-C levels, and increased hepatic lipase activity.

As shown in Table 3, the study of hepatic lipase and HDL levels was conducted in about 200 Turkish men and women in Istanbul and 60 Americans in San Francisco [26]. None of the subjects included in the study had triglycerides >200 mg/dl, and none was obese (body mass index <27 kg/m^2). The groups had comparable plasma cholesterol levels but, as expected, the Turkish men and women had lower HDL-C levels than the Americans. The Turkish men and women had slightly higher triglyceride levels,

Table 3. Characterization of Turkish and non-Turkish subjects*

	Men		Women	
	Turks (n=98)	Non-Turks (n=31)	Turks (n=116)	Non-Turks (n=29)
Age	39 ± 12	35 ± 7	36 ± 11	36 ± 7
Total Cholesterol (mg/dl)	178 ± 42	169 ± 32	182 ± 36	173 ± 28
Triglycerides (mg/dl)	119 ± 46**	83 ± 43	90 ± 36§	71 ± 30
HDL-C (mg/dl)	37 ± 9†	45 ± 11	43 ± 9#	58 ± 15
Hepatic Lipase (nmol/ml/h)	48.1 ± 16.1¶	38.8 ± 13.9	35.1 ± 12.3††	26.7 ± 7.9

Modified from reference 26. all values reported as mean ± SD.
***p = 0.0001, triglycerides higher in Turkish versus non-Turkish men.*
§p = 0.006, triglycerides higher in Turkish versus non-Turkish women.
†p = 0.0001, HDL-C lower in Turkish versus non-Turkish men.
#p = 0.00001, HDL-C lower in Turkish versus non-Turkish women.
¶p = 0.01, hepatic lipase higher in Turkish versus non-Turkish men.
††p = 0.0002, hepatic lipase higher in Turkish versus non-Turkish women.

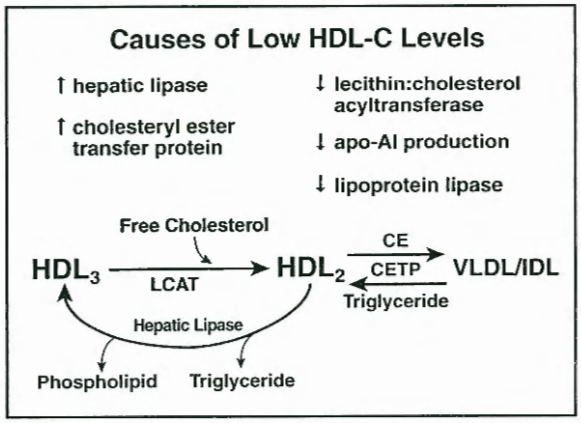

Figure 1. Various enzymes and transfer proteins are involved in the metabolism of HDL. Low levels of HDL-C are caused by high activity of hepatic lipase and the cholesterol ester transfer protein (CETP). Low levels of HDL-C are also caused by low activity of lecithin: cholesterol acyltransferase (LCAT) and lipoprotein lipase and by reduced synthesis of apolipoprotein (apo-) AI. IDL, intermediate density lipoproteins; CE, cholesteryl ester.

but none of the groups had mean triglycerides >120 mg/dl, and thus none were hypertriglyceridemic. Most strikingly, the activity of hepatic lipase stood out as being 25-30% higher in the Turks. Lipoprotein lipase activities were similar in the San Francisco and Istanbul men, but the Turkish women had lower levels than the American women [26]. The activities of the other factors were similar among the groups. Thus, the most remarkable finding consistently seen in the Turkish men and women was significantly elevated hepatic lipase activity.

The increase in hepatic lipase activity correlated significantly with low HDL_2 levels in the Turkish population [26]. The role of hepatic lipase was

independent of body mass index or triglyceride levels. We hypothesized that a promoter polymorphism in the gene could account for the increased expression of hepatic lipase in this population. In other studies, hepatic lipase activities account for 25-50% of the interindividual variation in HDL levels [27,28].

CLINICAL IMPORTANCE OF LOW HDL

Data from the Framingham Study demonstrate that CHD risk is 50% higher in subjects with HDL-C levels <35 mg/dl than in those with HDL-C levels >45 mg/dl [6,29,30]. Furthermore, Genest et al. [31] showed that low HDL-C was an extremely powerful predictor of premature CHD in a group of men studied angiographically. In ~60% of subjects with documented CHD, but in only 19% of controls without CHD, the HDL-C levels were <35 mg/dl. On the other hand, ~30% of the CHD subjects, but only 26% of the controls, had LDL-C >160 mg/dl. Thus, low HDL-C (<35 mg/dl) was almost twice as common as high LDL-C (>160 mg/dl) in patients with angiographically documented CHD.

The Framingham Study also clearly demonstrated that low HDL-C is a risk factor in the context of a normal or low plasma cholesterol level [10]. For example, men with low HDL-C (<40 mg/dl) but with a so-called normal plasma cholesterol level (<200 mg/dl) had an 11.2% incidence of CHD during 14 years of observation. This high incidence was identical to that seen in men with undesirably high plasma cholesterol levels (230-259 mg/dl) but who had somewhat higher HDL-C levels (40-49 mg/dl). However, the incidence of CHD dropped to 2.0% in men with plasma cholesterol levels of 230-259 mg/dl and HDL-C levels ≥60 mg/dl. Thus, low HDL-C is a powerful risk factor even in subjects with "normal" cholesterol levels, and high HDL-C levels can be protective in the context of elevated plasma cholesterol levels.

Therefore, in evaluating CHD risk, we must take into account total plasma cholesterol and HDL-C levels. In a low HDL-C population like Turkey, the total cholesterol/HDL-C ratio serves to focus our attention on both predictors of risk. As mentioned earlier, data from the Framingham study suggest that a total cholesterol/HDL-C ratio of ≤3.5 is ideal and that high risk results at a ratio >4.5 [9-11].

As illustrated in Table 2, American men, known to be at high risk, have a typical ratio of 4.5, whereas U.S. women have a ratio of 3.8. Similar ratios are seen in Germans. The high ratios in the American and European populations primarily reflect high levels of total plasma cholesterol due to high LDL-C levels. However, note that although the Turks tend to have lower total and LDL cholesterol levels, the very low HDL-C levels seen in this population result in high ratios. In fact, Turkish men and women in Germany or Istanbul tend to have ratios that are even higher than those seen in the high-risk Germans or Americans. Even in Ayvalık, where total cholesterol levels were very low, the ratios are still high because of the low HDL-C levels. The most undesirable total cholesterol/HDL-C ratios were seen in the Turks living in San Francisco (Table 2). These high ratios reflect the fact that the total cholesterol in these subjects was high even by U.S. standards and that the HDL-C levels were low.

We must ask the question of whether a low HDL-C is a risk factor in the presence of a "normal" cholesterol level in Turks. As mentioned previously, our present knowledge would suggest that the answer is yes. Therefore, a 10-15 mg/dl lower HDL-C level suggests that a desirable cholesterol level is lower than 200 mg/dl. For example, while most would agree that a total cholesterol of 180 mg/dl is excellent, one must take into account the effect of low HDL-C on the total cholesterol to HDL-C ratio. The "typical" Turkish man with an HDL-C of 35 mg/dl and a total cholesterol of 180 mg/dl would have a ratio of ~5.2 (undesirable). This same Turkish man with a cholesterol of 200 mg/dl would have a ratio of ~5.7 (clearly a high-risk ratio). Likewise, a Turkish woman with a "typical" HDL-C of 43 mg/dl and a total cholesterol of 180 mg/dl has a ratio of ~4.2. We must remember that the goal of a 200 mg/dl total cholesterol was established in populations where HDL-C levels were much higher than we see in Turks. A goal of a ratio of 3.5 may be unreasonable in Turkey; however, we must clearly factor into our guidelines and treatment goals the impact of low HDL-C, which is so highly prevalent in Turks.

TREATMENT OF PATIENTS WITH LOW HDL

Recent data indicate that it is beneficial to treat patients with low HDL in the context of relatively normal LDL-C levels. The CARE trial, a secondary prevention trial of pravastatin, showed a beneficial effect on CHD in patients with LDL-C of 139 mg/dl and HDL-C of 39 mg/dl [32]. Furthermore, the AFCAPS/TexCAPS trial, a primary prevention trial of lovastatin, demonstrated positive results in participants with average LDL-C (~156 mg/dl) and low HDL-C (37 mg/dl) [33]. These are lipid levels very commonly seen in the Turkish population.

The AFCAPS/TexCAPS trial was designed to determine if long-term therapy to reduce LDL-C would decrease the rate of the first acute major coronary event in a cohort of men and women with average LDL-C and low HDL-C. Approximately one-half of the more than 6,000 participants received 20 or 40 mg of lovastatin. The trial was stopped after 4.8 years because of very positive outcomes.

Treatment with lovastatin reduced LDL-C by 26% and increased HDL-C by 5% compared with the placebo group [33]. The lipid-lowering therapy reduced the total cholesterol/HDL-C ratio markedly from 6.3 to 4.8. Importantly, the treatment group had a 30-40% reduction in risk of myocardial infarction, unstable angina, the need for revascularization procedures, and other endpoints. For example, lipid-lowering therapy reduced the risk of a first acute major coronary event by 36%.

Results of this study may have special relevance in Turkey, where low HDL-C is a major problem. As AFCAPS/TexCAPS demonstrates, lowering LDL-C significantly decreased the total cholesterol/HDL-C ratio to a more desirable level and was associated with a clear reduction in CHD risk. The AFCAPS/TexCAPS investigators concluded that in conjunction with a prudent diet, regular exercise, and risk factor modification, drug therapy should be used to lower the risk of a first acute major coronary event in primary prevention candidates with the following characteristics: men >45 years of age or women >55 years who have HDL-C <50 mg/dl and LDL-C >130 mg/dl [33]. It is likely that new U.S. guidelines will take into account low HDL-C as an extremely important risk factor and will use the total cholesterol/HDL-C ratio to monitor treatment, especially in patients with low HDL-C. These considerations are extremely important in the context of the generalized low HDL-C levels seen in the Turkish population.

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