The Turkish Lipid Problem: Low Levels of High Density Lipoproteins

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The unique lipid and lipoprotein profile of Turks is characterized primarily by very low plasma levels of high density lipoprotein cholesterol (HDL-C), specifically low levels of the protective subclasses of HDL, HDL₂ and LpAI. The low HDL-C levels are associated with a 25–30% elevation of hepatic lipase activity that would be predicted to lower HDL levels. Low HDL-C levels occur in Turks living in Germany and the United States, suggesting that the reduced HDL-C levels are at least partly of genetic origin. Turkish girls and boys exhibit a marked 10–20 mg/dl drop in HDL-C levels associated with puberty, suggesting that the low HDL-C levels in Turks may reflect an ethnic difference in hormonal balance.

Data generated in the early 1990s in the original Turkish Heart Study and recently updated by a study of Turkish men and women living in Istanbul indicate that the lipid profile and other risk factors for coronary heart disease have not improved in this decade. Despite their relatively low plasma total cholesterol levels, Turks have extremely low HDL-C (<40 mg/dl in 70% of men and ~50% of women) resulting in very high total cholesterol/HDL-C ratios that predict increased coronary heart disease in other populations. The 2001 National Cholesterol Education Program guidelines continue to focus on low density lipoprotein cholesterol levels and underestimate the importance of low HDL-C levels, which undoubtedly are a powerful risk factor in Turks. We suggest that guidelines for Turkey consider both low density lipoprotein cholesterol levels and total cholesterol/HDL-C ratio as thresholds for initiating lifestyle changes or drug treatment for patients with coronary heart disease risk.

Key words: Coronary heart disease, hypercholesterolemia, high density lipoproteins, cholesterol metabolism, total cholesterol/HDL-C ratio

Introduction

Coronary heart disease (CHD) and other atherosclerosis-related vascular diseases account for the majority of deaths in most industrialized and developing countries. However, the major risk factors are well known, and most premature CHD (morbidity and mortality before 65 years of age) could be prevented if patients at risk were properly managed.
The major known risk factors are elevated levels of low density lipoprotein cholesterol (LDL-C), reduced levels of high density lipoprotein cholesterol (HDL-C), cigarette smoking, hypertension, type 2 diabetes mellitus, obesity, and a family history of premature (men <55 years; women <65 years) CHD events in a first-degree relative (1). Observational studies suggest that modifiable risk factors account for 85% of excess risk for premature CHD (2,3). When total cholesterol levels are below 160 mg/dl, CHD risk is markedly reduced even in the presence of additional risk factors suggesting that morbidity and mortality from atherosclerotic vascular disease largely result from hyperlipidemia or dyslipidemia (4). The major cause of increased atherogenic risk is hypercholesterolemia, and both genetic disorders and diets enriched in saturated fat and cholesterol contribute to the elevated lipid levels characteristic of patients with premature CHD. There is now universal acceptance of the cholesterol-diet-CHD hypothesis (5).

Hypercholesterolemia, especially elevated plasma LDL-C levels, has been the focus of much attention because cholesterol levels can be effectively reduced by drug therapy. In extensive, well-controlled studies of patients with elevated LDL-C levels, CHD mortality has been reduced by as much as 30-40% over a relatively short period (~5 years) (6-8). There is every reason to believe that far better results can be achieved with more aggressive lipid lowering over longer periods of time.

In 2002, we realize that dyslipidemic treatment guidelines must not be based on absolute values of LDL-C alone. Management of risk demands that we also consider the impact of low plasma HDL-C levels. Clinical trial data demonstrate that high risk is associated with reduced levels of HDL-C even if the LDL-C levels are low. Patients with low HDL-C and so-called normal LDL-C levels benefit from initiating hypolipidemic drug therapy (9). Appropriate drug therapy reduced CHD endpoints in low HDL-C patients by 20-35% (10,11). Since low HDL-C is present in 40% of patients with CHD in the United States (12) and is widely prevalent in Turkey (13), it is obvious that treatment guidelines should reflect the risk associated with low HDL-C even if LDL-C levels are considered to be in the "normal" range.

The importance of hypertriglyceridemia as an independent CHD risk factor may be debatable, but moderately elevated levels of triglycerides (typically, 250-500 mg/dl) are often associated with the atherogenic dyslipidemia that occurs as part of the metabolic syndrome (1). The metabolic syndrome is characterized by low HDL-C levels and lipid-depleted small, dense LDL and is associated with insulin resistance, obesity, hypertension, and a hypercoagulable state (14,15). The metabolic syndrome is common in CHD patients; therefore, the identification of moderate hypertriglyceridemia, even if the total cholesterol level is normal, should trigger a careful evaluation and treatment of this potentially atherogenic disorder (1). The age-adjusted prevalence of the metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP) (1), is 23.7% in the United States.

Although controlling other CHD risk factors (i.e., smoking, hypertension, obesity, and diabetes) is very important, treatment of dyslipidemia can markedly reduce CHD risk. In this review we focus on dyslipidemia and on the unique lipid and lipoprotein profile in the Turkish population.

The Turkish Lipid Problem

The Turkish population has a unique lipoprotein profile that would be predicted to be associated with an increase in CHD risk (13). Several studies have now confirmed that HDL-C levels in Turks are among the lowest in the world and are 10-15 mg/dl lower than those in western European or U.S. populations (13, 16-20). Low HDL-C levels are proatherogenic and are associated with a high incidence of CHD (21-25).

The Turkish Heart Study: The Turkish Heart Study, which began in 1990, has evaluated plasma lipids and lipoproteins in Turks in various regions of Turkey (13), Germany (26), and the U.S. (27, 28). In the initial population survey conducted in 1990-1993, Turks in six regions of Turkey were found to have relatively low total cholesterol (~160-190 mg/dl) and LDL-C (~100-130 mg/dl) levels (13), in agreement with results from other studies (18,29). The variability in plasma total cholesterol and LDL-C levels correlated primarily
with the predominant type of fat being consumed in the various regions. The lowest total cholesterol levels were seen in individuals living in and around Ayvalık, where olive oil, which is rich in the cholesterol-lowering monounsaturated fats, is widely consumed. Cholesterol levels were higher in the regions where meat and dairy products, which are rich in saturated fats, are widely consumed. Interestingly, the more affluent men and women had the highest total cholesterol and LDL-C levels, which were associated with the higher consumption of saturated fats. The highest cholesterol levels were likewise seen in urban populations, as opposed to rural populations. Importantly, Istanbul men and women had mean cholesterol levels similar to those seen in high-risk western populations.

On the other hand, HDL-C levels were low in all regions of the country, were not significantly affected by the dietary differences, and did not correlate with affluence or socioeconomic status (SES). The HDL-C levels were extremely low (mean, 36 mg/dl in men and 42 mg/dl in women) by comparison with other populations and were not explained by any metabolic or environmental factors, suggesting a genetic origin.

Istanbul Participants Ñ Original and Updated Turkish Heart Study: We have continued to monitor the plasma lipids and lipoproteins of the high-risk Istanbul men and women. Table 1 summarizes the data from the original study (1990-1993) and a recent updated study. In the Istanbul men, the average total cholesterol and LDL-C levels were similar in both studies (~200 and 130 mg/dl, respectively). The HDL-C levels were also essentially identical in both studies (36-38 mg/dl), and the total cholesterol/HDL-C ratio reflected high risk (~5.5). The recent data suggested a trend toward higher fasting triglyceride levels in the men. The Istanbul women appeared to have a similar trend toward slightly higher total cholesterol and LDL-C levels in the recent survey (Table 1). The mean HDL-C levels for the women were ~46 mg/dl in the original study and 42 mg/dl in the recent study. The total cholesterol/HDL-C ratio in the original survey was 3.9; now it is 4.8, which reflects the lower HDL-C levels in the Istanbul women.

The effects of age and body mass index (BMI) or lipid values in the Istanbul men and women in both studies are shown in Table 1. Total cholesterol and LDL-C levels increased markedly with age, but HDL-C levels were unchanged. A high BMI has negative effects on plasma lipids, and recent data demonstrate that increasing BMI is a problem both in the United States and in Turkey. In the updated Turkish Heart Study, 66% of the men and 49% of the women were overweight (BMI >25 kg/m²). In the United States, more than 50% of the population is overweight, and 20% of the men and 25% of the women are obese (BMI >30 kg/m²). Onat et al. reported a similar prevalence of obesity in Turkish men (~19%), but found an alarmingly high prevalence of obesity in Turkish women (~39%). An elevated BMI has many detrimental effects on health, but especially an increased risk of CHD. As BMI increased in the Turkish men and women (Table 1), total cholesterol, LDL-C, and triglyceride levels increased markedly whereas HDL-C levels decreased. Remarkably, the total cholesterol/HDL-C ratio in the most recent data rose from 5.4 in men with normal BMI to 6.8 in obese men and from 4.2 in women with normal BMI to 5.8 in obese women. Thus, in the low HDL-C Turkish population, BMI appears to have a major effect on risk, suggesting that overweight and obesity should be considered as CHD risk factors.

Table 2 illustrates the extent of low HDL-C and elevated total cholesterol/HDL-C ratio in the Turkish population. Low HDL-C levels were previously defined as <35 mg/dl; more recently, low HDL-C levels have been defined as <40 mg/dl. In the update study of the Istanbul population, 53% of men and 20% of women had HDL-C levels <35 mg/dl. In comparison, only about 15% of U.S. men and 5% of U.S. women have such low HDL-C levels. The impact of changing the definition of low HDL-C to <40 mg/dl is astounding. Under the new U.S. guidelines, 77% of Turkish men and 48% of Turkish women living in Istanbul have low HDL-C levels. Analysis of the original Turkish Heart Study data revealed very similar data for Turks throughout the country (74% of the men and 53% of the women had HDL-C levels <40 mg/dl).

Because of their very low HDL-C levels, Turks tend to have very high total cholesterol/HDL-C...
factors is suggested by the observation that HDL-C levels were low in all regions of Turkey despite very different dietary habits (13). Furthermore, low HDL-C levels were observed in Turks living in Germany, some of whom had been living in Germany for many years (Table 3) (26). The most compelling data come from studies of Turks living in San Francisco, California, who also had low HDL-C levels (27) (Table 3). In addition, wives of Turkish men living in San Francisco, who were of western European ancestry, did not have low HDL-C, but had values typical of other U.S. women. Evaluation of common environmental factors did not explain the 10-15 mg/dl lower HDL-C levels seen in the Turks (13,27,28). Nevertheless, it is well known that various factors, such as smoking, lack of physical activity, obesity, and diets that elevate triglyceride levels, can lower HDL-C levels (1,25). All these factors are prominent in Turkey and could be acting in concert to exacerbate the genetically determined low HDL-C problem.

**Mechanism Responsible for Low HDL-C in the Turkish Population:** The possibility that the low HDL-C levels in Turks reflect underlying genetic

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**Table 1.** Plasma lipids and lipoproteins in the original and updated Turkish Heart Study (THS): Effects of age and BMI

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>Total Cholesterol/HDL-C Ratio</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Original THS</td>
<td>All ages</td>
<td>2119</td>
<td>527</td>
<td>201 ± 45</td>
<td>173 ± 40</td>
<td>136 ± 40</td>
</tr>
<tr>
<td></td>
<td>20–40 years</td>
<td>1210</td>
<td>439</td>
<td>189 ± 44</td>
<td>165 ± 33</td>
<td>127 ± 39</td>
</tr>
<tr>
<td></td>
<td>&gt;40 years</td>
<td>909</td>
<td>88</td>
<td>216 ± 41</td>
<td>210 ± 47</td>
<td>148 ± 37</td>
</tr>
<tr>
<td>Update THS</td>
<td>All ages</td>
<td>196</td>
<td>209</td>
<td>197 ± 46</td>
<td>191 ± 50</td>
<td>126 ± 38</td>
</tr>
<tr>
<td></td>
<td>20–40 years</td>
<td>102</td>
<td>116</td>
<td>186 ± 44</td>
<td>169 ± 39</td>
<td>120 ± 37</td>
</tr>
<tr>
<td></td>
<td>&gt;40 years</td>
<td>94</td>
<td>93</td>
<td>209 ± 46</td>
<td>219 ± 49</td>
<td>133 ± 38</td>
</tr>
<tr>
<td>Original THS</td>
<td>BMI &lt;25 kg/m²</td>
<td>912</td>
<td>356</td>
<td>189 ± 42</td>
<td>167 ± 38</td>
<td>128 ± 38</td>
</tr>
<tr>
<td></td>
<td>25–29 kg/m²</td>
<td>912</td>
<td>121</td>
<td>208 ± 44</td>
<td>183 ± 40</td>
<td>141 ± 40</td>
</tr>
<tr>
<td></td>
<td>&gt;30 kg/m²</td>
<td>170</td>
<td>38</td>
<td>215 ± 46</td>
<td>184 ± 40</td>
<td>146 ± 40</td>
</tr>
<tr>
<td>Update THS</td>
<td>BMI &lt;25 kg/m²</td>
<td>68</td>
<td>106</td>
<td>193 ± 51</td>
<td>174 ± 47</td>
<td>127 ± 42</td>
</tr>
<tr>
<td></td>
<td>25–29 kg/m²</td>
<td>101</td>
<td>60</td>
<td>192 ± 40</td>
<td>203 ± 49</td>
<td>223 ± 49</td>
</tr>
<tr>
<td></td>
<td>&gt;30 kg/m²</td>
<td>27</td>
<td>42</td>
<td>224 ± 45</td>
<td>214 ± 47</td>
<td>143 ± 35</td>
</tr>
</tbody>
</table>

*Values for lipid levels and BMI are mean ± SD.

<table>
<thead>
<tr>
<th>HDL-C (mg/dl)</th>
<th>Total Cholesterol/HDL-C Ratio</th>
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<tbody>
<tr>
<td>&lt;30</td>
<td>&lt;35</td>
</tr>
<tr>
<td>&lt;4.5</td>
<td>4.5–5.9</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Men (n = 196)</th>
<th>16%</th>
<th>53%</th>
<th>77%</th>
<th>28%</th>
<th>34%</th>
<th>39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n = 209)</td>
<td>3%</td>
<td>20%</td>
<td>48%</td>
<td>53%</td>
<td>28%</td>
<td>19%</td>
</tr>
</tbody>
</table>
disease, whereas low HDL-C levels represent a powerful risk factor (21-25,41). HDL participate in a process known as reverse cholesterol transport in which HDL transport excess cholesterol from cells, including cholesterol-loaded macrophages in the artery wall, to the liver for excretion from the body. Various enzymes and transfer proteins acting upon HDL are involved, and an abnormality at any step can cause a defect in the process and alter the levels of HDL and the subclasses of HDL (for review, see references 41-45).

Pre-β HDL are lipid-poor precursors of mature HDL particles (Figure 1). As the pre-β HDL acquire free cholesterol from cells, they are converted to the small, spherical particles called HDL3. The free cholesterol is converted by the enzyme lecithin: cholesterol acyltransferase to cholesterol esters that form the core of the HDL particle. As more free cholesterol is acquired and becomes esterified, the particles increase in size and are converted to HDL2 particles. The excess cholesterol esters are.

<table>
<thead>
<tr>
<th></th>
<th>Americans in U.S.A</th>
<th>Germans in Germany</th>
<th>Turks in Turkey</th>
<th>Turks in Germany</th>
<th>Turks in San Francisco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>47</td>
<td>47</td>
<td>37</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Women</td>
<td>56</td>
<td>60</td>
<td>43</td>
<td>45</td>
<td>46</td>
</tr>
</tbody>
</table>

between triglyceride and HDL-C levels is also present in the Turkish population; however, the low HDL-C levels in Turks are not explained by elevated triglyceride levels. For example, Danish men in the Copenhagen Male Study (39) who had triglyceride levels <100 mg/dl had mean HDL-C levels of 61 mg/dl whereas Turkish men from the Turkish Heart Study (13,27,28) and the Turkish Adult Risk Factor Study (40) with the same triglyceride levels had HDL-C levels of 40-41 mg/dl. Similarly, triglyceride levels of 100-139 mg/dl in Turks and Danes are associated with HDL-C levels of 37-38 mg/dl and 52 mg/dl, respectively. Furthermore, Framingham data describing the relationship between triglyceride and HDL-C in U.S. men and women (21) demonstrate that Turks have HDL-C levels that are typically 10-15 mg/dl lower over a triglyceride range of 50-200 mg/dl.

Metabolism of HDL: Epidemiological and clinical studies have demonstrated that higher levels of HDL-C are protective against atherosclerotic vascular disease, whereas low HDL-C levels represent a powerful risk factor (21-25,41). HDL participate in a process known as reverse cholesterol transport in which HDL transport excess cholesterol from cells, including cholesterol-loaded macrophages in the artery wall, to the liver for excretion from the body. Various enzymes and transfer proteins acting upon HDL are involved, and an abnormality at any step can cause a defect in the process and alter the levels of HDL and the subclasses of HDL (for review, see references 41-45).

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**Figure 1.** HDL levels in the plasma are controlled by numerous enzymes and transfer proteins that act on the different subclasses of HDL. CE, cholesterol ester; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins.
transferred to very low density lipoproteins (VLDL) and LDL by the cholesterol ester transfer protein. The VLDL and LDL are ultimately removed from the plasma by the liver, and in this indirect way the excess cholesterol acquired from cells by the HDL is delivered to lipoproteins taken up by the liver and is excreted in the bile and eliminated from the body. As the cholesterol ester transfer protein transfers cholesterol esters from HDL to VLDL and LDL, it also transfers triglycerides to the HDL$_2$ particles to replace the cholesterol esters. The HDL$_2$ particles are then acted upon by hepatic lipase to hydrolyze the excess triglycerides and in the process are converted to HDL$_3$ (Figure 1). The newly regenerated HDL$_3$ can acquire more cholesterol from cells and repeat the transport cycle.

As discussed, high levels of some factors can cause low HDL-C levels, whereas low levels of others can also have this effect (41-44). Examination of the activities of the various factors controlling HDL metabolism demonstrated that Turks have 25-30% greater hepatic lipase activity than U.S. (white American) men and women (27). Increased hepatic lipase activity lowers HDL-C levels (25, 45,46).

Isolation and characterization of the HDL subclasses in Turks revealed lower levels of HDL$_2$, lower levels of LpAI (a subclass resembling HDL$_2$), and higher levels of a subclass known as LpAI/AII than in western European or U.S. populations (28). These changes would be predicted to be proatherogenic. Because they are better acceptors of cholesterol, HDL$_2$ and LpAI are more protective subclasses than HDL$_3$ or LpAI/AII (22,47-49). In addition, particles with apolipoprotein AII, such as LpAI/AII, are associated with an increased risk of atherosclerosis (50,51). Thus, low levels of the protective HDL$_2$ and LpAI subclasses characterize the HDL-C of Turks associated with elevated hepatic lipase activity.

The cause of the increased hepatic lipase activity has not been elucidated. We hypothesized that a unique promoter polymorphism in the hepatic lipase gene in Turks might enhance the synthesis of the enzyme. To date, we have not identified a polymorphism that could account for the increased activity. However, testosterone is a major regulator of hepatic lipase (52-54). Hergenç and associates showed that Turks have lower levels of sex hormone binding globulin than Germans and hypothesized that the lower levels of this protein could be associated with increased levels of free bioactive testosterone in Turks (20). High levels of free testosterone could upregulate hepatic lipase activity. We believe the dynamic balance in levels of hormones such as androgens, estrogens, leptin, and insulin may be altered in Turks.

**Impact of Puberty, Socioeconomic Status, and Nutrition on Plasma Cholesterol and HDL-C Levels in Turks:** In western European and U.S. populations, plasma lipids change markedly with age and at puberty (55-63). At birth, plasma total cholesterol and HDL-C levels are low (<100 and ~30 mg/dl, respectively), and there are no gender differences. By ~8-10 years of age, total cholesterol and HDL-C levels have increased, typically to 140-160 mg/dl and ~55-60 mg/dl, respectively, in both males and females. After puberty, total cholesterol levels continue to increase, more in males than in females, but HDL-C levels decrease by 8-10 mg/dl in males (to adult levels of 46-48 mg/dl) and by only ~2 mg/dl in females (to ~56-58 mg/dl).

To determine whether HDL-C levels in Turks are low from birth to adulthood and to assess the effects of puberty on HDL-C levels, we recently studied Turkish newborns and prepubescent school children (16). Healthy Turkish newborns had plasma total cholesterol and HDL-C levels similar to those in other populations (~60 and ~30 mg/dl, respectively), and there are no gender differences. By ~8-10 years of age, total cholesterol and HDL-C levels have increased, typically to 140-160 mg/dl and ~55-60 mg/dl, respectively, in both males and females. After puberty, total cholesterol levels continue to increase, more in males than in females, but HDL-C levels decrease by 8-10 mg/dl in males (to adult levels of 46-48 mg/dl) and by only ~2 mg/dl in females (to ~56-58 mg/dl).

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Figure 2. After puberty, the HDL-C levels decreased by ~20 mg/dl in the upper SES boys and by ~13 mg/dl in the upper SES girls (16). These puberty-associated decreases in HDL-C are much greater than those in other populations (Figure 2), suggesting that hormonal changes at puberty affect HDL metabolism differently in Turks than in populations with higher HDL-C levels. SES was associated with HDL-C differences in prepubescent Turkish children, but had no effect on HDL-C after puberty or throughout adulthood in Turkish men and women (13,16). It remains to be determined if the modulation of HDL-C at puberty involves androgens, estrogens, leptin, insulin, or other hormones.

**Table 4.** Mean plasma lipid levels (mg/dl ± SD): Upper and lower socioeconomic status (SES) children 8–10 years of age

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol</th>
<th></th>
<th>HDL-C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>Total</td>
<td>138 ± 26</td>
<td>143 ± 26</td>
<td>50 ± 13</td>
<td>49 ± 12</td>
</tr>
<tr>
<td>Upper SES</td>
<td>154 ± 20</td>
<td>158 ± 25</td>
<td>58 ± 14</td>
<td>55 ± 12</td>
</tr>
<tr>
<td>Lower SES</td>
<td>129 ± 25</td>
<td>134 ± 22</td>
<td>45 ± 10</td>
<td>45 ± 10</td>
</tr>
</tbody>
</table>

was explained by a 10% greater consumption of fat, primarily animal (saturated) fat, in the diets of the upper SES children. Diets rich in saturated fat are known to increase plasma cholesterol levels (64,65). The HDL-C levels were 10-13 mg/dl lower in lower SES boys and girls than in upper SES children (Table 4). This difference was explained by the higher consumption of carbohydrates by the lower SES children (~60% versus 50% of total calories). High-carbohydrate diets are known to cause low HDL-C levels (61,65-67).

The upper SES children consumed diets very similar to those of western European and U.S. children and had virtually identical lipid levels (total cholesterol, ~155 mg/dl; HDL-C, 55-58 mg/dl) (Figure 2). The uniqueness of the Turkish lipid profile raises the question of whether the NCEP (1) or European (68) guidelines are appropriate for Turks with low HDL-C. These guidelines were developed for populations in which >70% of the individuals have HDL-C levels >40 mg/dl. However, at least 70% of the men and 50% of the women in Turkey have HDL-C levels <40 mg/dl. In our opinion, these guidelines do not take into account the widespread

**Figure 2.** Changes in plasma HDL-C levels with age in western European and U.S. populations versus the upper SES Turkish population. A profound decrease in HDL-C levels in Turkish men and women is observed (see reference 16 for more detail).
prevalence of low HDL-C or the increased risk associated with a progressive decrease in HDL-C levels. Thus guidelines that are unique for populations with low HDL-C need to be developed.

Since low HDL-C is a powerful risk factor for CHD (21-25,69) and since low HDL-C is so widespread in Turks (13,27,28), we must ask what parameters are most appropriate to guide treatment of hyperlipidemia in this population. Clearly, elevated levels of total cholesterol and LDL-C levels are predictive of increased risk, and lowering the levels confers great benefit (6-11,70-74). However, what about the majority of Turkish patients who have "normal" total cholesterol (<200 mg/dl) and LDL-C (<130 mg/dl) levels but also may have extraordinarily low HDL-C levels (<40 mg/dl)? The typical Turkish man with a total cholesterol of 180 mg/dl would be considered to have an ideal level, but if he has an HDL-C of 30 mg/dl, is he at risk of CHD? It is likely that his LDL-C is ~120 mg/dl (a desirable level). The preponderance of evidence indicates that he is at risk despite a normal total cholesterol and a normal or low LDL-C. Data from the Framingham study (37) indicate that the incidence of CHD is higher in patients with a total cholesterol <200 mg/dl and an HDL-C <40 mg/dl than in patients with a total cholesterol of >260 mg/dl and an HDL-C of 50-59 mg/dl (11.2% versus 9.0%). Individuals with total cholesterol >260 mg/dl but with HDL-C >60 mg/dl have a CHD incidence of 3.8%. Thus, we suggest that both total cholesterol and HDL-C must be taken into account, especially in patients with low HDL-C levels. Therefore, the best parameter for monitoring CHD risk in Turkish patients is likely to be the total cholesterol/HDL-C ratio. This suggestion is consistent with results presented by Onat (19). The Framingham study demonstrated that a total cholesterol/HDL-C ratio of 5 to 5.5 predicts a 10% CHD risk and therefore necessitates therapy (37, 38). In the PROCAM study, the incidence of myocardial infarction over a 10-year period was 10.7% at a ratio >5.0, but was only 3.1% at a ratio ≤5.0 (75). In Turkish patients with low HDL-C, we would suggest that a total cholesterol/HDL-C ratio >5 to 7 should be used to indicate increased risk even if they have a normal LDL-C. If multiple risk factors are present, treatment should be considered at even lower ratios.

**Simplified Guidelines for Low HDL-C Populations:** As outlined in Table 5 (modified from reference 30), the risk categories include CHD or the equivalent (defined as any vascular disease problem or diabetes), 2+ risk factors, or 0-1 risk factor. The risk factors are defined by the 2001 NCEP guidelines, but in addition we would include overweight, defined as a BMI >25 kg/m² and a waist circumference of 102 cm (men) or 88 cm (women) (1). We do not believe that most physicians will use the Framingham risk tables; therefore, we do not include the risk calculations. We suggest that the total cholesterol/HDL-C ratio be used in concert with LDL-C to determine how to manage patients with low HDL-C. Because of their relatively low LDL-C levels, many Turkish patients simply do not meet the LDL-C criteria for treatment by the NCEP guidelines. However, several recent clinical trials have demonstrated that low HDL-C patients with low or normal LDL-C benefit from lipid-lowering therapy (10,11,71-76). CHD or equivalent patients need to have a target LDL-C <100 mg/dl. The recent Heart Protection Study suggests that CHD patients with LDL-C <100 mg/dl at baseline benefited from drug treatment to the same extent as those with LDL-C >100 mg/dl at baseline (73,74,77). Therefore, a target of 100 mg/dl is probably still too high. In CHD or equivalent patients with very low HDL-C

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Goals</th>
<th>Lifestyle Change Initiated for</th>
<th>Drug Therapy Initiated for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C</td>
<td>TC/HDL-C</td>
<td>LDL-C</td>
</tr>
<tr>
<td>CHD or equivalent</td>
<td>&lt;100</td>
<td>&lt;3.5</td>
<td>≥100</td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>&lt;130</td>
<td>&lt;4.5</td>
<td>≥130</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;160</td>
<td>&lt;5.5</td>
<td>≥160</td>
</tr>
</tbody>
</table>

*To decrease the number of individuals requiring drug treatment, these risk categories could be further restricted to men ≥45 years of age and to women ≥55 years of age. TC, total cholesterol.
it is probably important to attain a total cholesterol/HDL-C ratio <3.5 for maximum benefit.

These simplified treatment guidelines use the same LDL-C target for initiating treatment as the NCEP, but also use the total cholesterol/HDL-C ratio to determine if lifestyle change or drug therapy should be recommended (Table 5). The initiation of drug therapy can be further restricted by age (≥45 years for men; ≥55 years for women). This restriction limits the number of individuals requiring drug treatment to the higher-risk age group. These are suggestions, but as always, clinical judgment concerning the magnitude of overall risk, as well as other considerations unique to the individual patient, will contribute to the therapeutic decision.

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