Lipids, Lipoproteins and Apolipoproteins Among Turks, and Impact on Coronary Heart Disease

Türk Halkında Lipid, Lipoprotein ve Apolipoproteinler ile Bunların Koroner Arter Hastalığı'na Etkileri

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ABSTRACT

Serum concentrations of lipids, lipoproteins, and apolipoproteins (apo) among Turkish adults have been reviewed in this paper whereby stratification by gender and age groups was provided, together with a description of differences by geographic regions and urban-rural areas. Most of the knowledge was derived from the prospective population-based Turkish Adult Risk Factor (TEKHARF) Study, having already a 13 years' follow-up, but data contributed by the Turkish Heart Study were also outlined.

In the setting of a prevalence of metabolic syndrome in 3 out of 8 Turkish adults, Turks have low levels of total cholesterol (mean 185 mg/dl), LDL-cholesterol (mean 116 mg/dl), and HDL-cholesterol (mean 37 and 45 mg/dl in men and women). The latter is associated with comparatively high concentrations of triglycerides (mean 143 mg/dl) and of apo B (mean 115 mg/dl). This suggests that small, dense LDL particles (pattern B) prevail in this population though studies are missing in this regard. In line with this notion are the high levels of total/HDLcholesterol ratio (mean 5.3 in men, 4.5 in women). It is remarkable that women exhibit identical LDL-cholesterol levels as men. The lipid parameter that has changed strikingly since 1990 are the rising triglycerides, accompanying a similar trend in (abdominal) obesity.

On multivariate analysis, the best independent lipid predictor of coronary heart disease (CHD) risk among Turks is the TC/HDL-C ratio. A 2-unit increment of TC/HDL-C adds an excess of 68% to both the nonfatal and fatal CHD event risk. When ratios of ≥5.5 in men and ≥5 in women are considered as high risk, slightly more than one-third of Turkish adults, corresponding to 12 million adults, are included by these criteria into high-risk group. A major portion of Turkish adults harbouring total cholesterol concentrations in the 180-200 mg/dl range are at high risk, and we stress the opinion that the upper normal limit of total cholesterol be reduced to 180 mg/dl in Turks, at least in men. *(Anadolu Kardiyol Derg 2004; 4: 236-45)*

Key words: Coronary heart disease, lipid, lipoprotein, apolipoprotein

ÖZET

Bu gözden geçiride Türk yetişkinlerinde lipid, lipoprotein ve apolipoproteinler (apo) ile ilgili serum konsantrasyonları, cinsiyet ve yaş gruplarına katmanlanarak ve coğrafi bölge ile kırsal-kentsel kesim farkları dikkate alınarak özetlendi. Bilgilerin çoğu için, 13 yıllık bir izlemeyi geride bırakan, popülasyona dayalı TEKHARF Çalışması verileri temel alındı, ama Türk Kalp Çalışmasının katkıları da belirtildi.

Her 8 Türk erişkininden üçünün metabolik sendroma sahip olması çerçevesinde, Türkler düşük total kolesterol (ortalama 185 mg/dl), LDL-kolesterol (ort. 116 mg/dl) ve HDL-kolesterol (erkekle kadında ort. 37 ve 45 mg/dl) düzeyleri barındırmaktadır. Sonuncu değere yüksek trigliserid (ort. 143 mg/dl) ve apo B (ort. 115 mg/dl) konsantrasyonları eşlik etmektedir. Bu durum, doğrudan incelemelerin eksik olmasına rağmen, halkımızda küçük, yoğun LDL parçacıklarının (B patterni) yaygın olduğuna işarettir. Bu görüşle uyum sağlayacak biçimde, total/HDL kolesterol oranı (ort. erkekte 5.3, kadında 4.5) yüksektir. Kadınlarda LDL-kolesterol değerlerinin erkektekinden düşük olmadığı dikkat çekicidir. Bin dokuz yüz doksan yılından beri en çarpıcı biçimde değişen lipid parametresi, (abdominal) obezitede görülen eğilime paralellik sergileyen, yükselen trigliseridler olmuştur.

Yetişkinlerimizde koroner kalp hastalığının (KKH) çok değişkenli analizde en iyi lipid öngördürücüsü total/HDL kolesterol oranıdır. Bu oranda 2 birimlik bir artış, fatal ve nonfatal KKH riskini %68 yükseltmektedir. Oranın erkekte ≥5.5, kadında ≥5 olmasının yüksek risk olarak alınması halinde, yetişkinlerimizin üçte birini aşan ve yaklaşık 12 milyona varan bir bölümünün bu kapsama girdiği anlaşılmaktadır. Total kolesterol konsantrasyonları 180-200 mg/dl bulunan yetişkinlerimizin önemli bir bölümünün yüksek risk altında olduğu göz önünde tutulursa, Türk erişkinlerinde, hiç değilse erkeklerimizde, normal kolesterol üst sınırının 180 mg/dl altına çekilmesi gerektiği inancımızı yeniden vurgulamakta yarar görüyoruz. *(Anadolu Kardiyol Derg 2004; 4: 236-45)*

Anahtar kelimeler: Koroner kalp hastalığı, lipid, lipoprotein, apolipoprotein

Introduction

This review deals with levels of lipids, lipoproteins, and apolipoproteins, stratification by gender and age groups among Turkish adults, along with a description of differences by geographic regions and urban-rural areas. It will necessarily be based on the data of the Turkish Adult Risk Factor (TEKHARF) Study, but data of the Turkish Heart Study will be utilized as well. Attempt will be made

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to provide these in the perspective of features in Western societies. Changes and trends over the past decade will be underlined; the associations of lipids with certain other risk factors will be analyzed. The value in coronary heart disease (CHD) prediction of the levels of lipids, lipoproteins and apolipoprotein B and C-III will be discussed, based on the findings of the TEKHARF Study, comparing with observations in Western populations.

It would not be unjust to state that very little was known prior to 1990 on lipids and lipoprotein levels among Turkish adults, including the basic knowledge that even the total cholesterol levels were generally low, except for clinical impressions that high concentrations (at the time >240 mg/dl) were rarely encountered even in patients with definite or suspected CHD.

The nationwide TEKHARF Study conducted in 1990 provided first published data, followed by publications in local (1) and international periodicals (2) pointing to the low total cholesterol levels.

Methods and Participants of the TEKHARF Study

Enrolled was a sample of 3687 persons to represent the Turkish population aged 20 years or over stratified for gender, age groups, size of communities and urban-rural distribution. Thus, 59 communities (32 urban and 27 rural) scattered over all 7 geographic regions had taken part in the sample (3).

Total cholesterol and triglyceride concentrations were measured enzymatically in plasma using Böhringer Mannheim kits and a Reflotron apparatus. Triglycerides were measured only in participants applying in the postabsorptive period. Validation of data was performed in a reference laboratory in approximately 6% of venous blood samples, and the required adjustments were made.

A printed questionnaire containing information on the past history of the participant, physical examination findings of the cardiovascular system, laboratory analyses and a resting electrocardiogram (ECG) formed the data. Diagnosis of CHD was based on a history of typical exertional angina, myocardial infarction or revascularization and on Minnesota coding of the ECG for myocardial infarction and ischemia (4) as previously described (5). Median age was 37 years.

Levels of Total Cholesterol

Mean concentrations of total cholesterol, age-standardized according to the World Health Organization for the age bracket 35-64 years, were 185 mg/dl in men, and 192 mg/dl in women (2). The distribution of plasma cholesterol and triglyceride levels by gender and age groups is presented in the Table 1. While low cholesterol levels are seen in the age group 20-29, a plateau of 188 mg/dl is reached in men in their 40s, and women attained levels of 204 mg/dl in the following life-decades. Mean total cholesterol concentrations were not only far lower than in populations of the Northern Europe, but even lower than in the Mediterranean populations. As the mean level in residents of communities comprised in the MONICA project was 234 mg/dl, it is gratifying for Turks to know to possess levels 40-50 mg/dl lower.

Tablo 1. Distribution of plasma cholesterol and triglyceride levels (mg/dl) by gender and age groups.

	Men		Women	
Age groups	Cholesterol	Triglyceride	Cholesterol	Triglyceride
20-29	148 ± 35	106 ± 67	153 ± 35	59 ± 49
30-39	174 ± 38	150 ± 99	171 ± 36	106 ± 63
40-49	188 ± 41	163 ± 101	188 ± 39	125 ± 68
50-59	189 ± 44	143 ± 88	204 ± 40	137 ± 83
60-69	184 ± 43	131 ± 79	204 ± 45	157 ± 93
>70	177 ± 39	115 ± 50	194 ± 34	142 ± 86

The stratification of mean total cholesterol values by age groups, sex and urban-rural distribution is graphically illustrated in Fig. 1. Turkish adults take off in life with levels as low as 150 mg/dl at age group 20-29, but reach rapidly concentrations of 188 mg/dl within only two decades. This rise by 25% appears to be unique when compared with other populations. It may be estimated that the steep rise is secondary to diminution of low density lipoproteins catabolism associated with hormonal changes due to aging (6).

It has been repeatedly demonstrated in the TEKHARF study that women exhibit consistently higher cholesterol values than Turkish men from age 50 onwards. Among subjects past the age 40 years, women harboured 9.6 mg/dl higher levels than men even in urban areas, the difference rising to 14.4 mg/dl in rural areas ($p<0.01$).

Urban-rural areas: Average total cholesterol values in urban residents exceeded those of rural inhabitants from age 40 onwards: by 13.5 mg/dl in men, by 8.4 mg/dl in women ($p<0.01$).

Regional Distribution of Cholesterol Levels

The distribution across regions of mean cholesterol concentrations in men and women aged 40-59 are seen in the Table 2. "High" levels existed in the Marmara (201 mg/dl), Black Sea (196 mg/dl) and Aegean regions (195 mg/dl), while the Mediterranean region revealed the lowest levels (172 mg/dl).

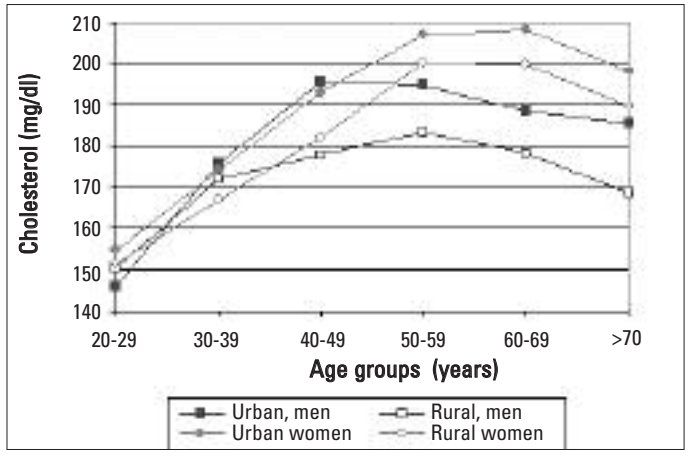


Figure 1. Mean total cholesterol levels among Turkish adults in urban and rural areas, by age groups, in year 1990 (adapted from Ref. 2)

Tablo 2. Regional distribution of mean cholesterol concentrations among 40-59 years men and women

	Men			Women		
Regions	n	mean	SD	n	mean	SD
Marmara	138	199	42	133	204	39
Black Sea	64	197	42	64	195	39
Aegean	82	191	46	82	200	39
Central Anatolia	126	191	42	122	194	35
Eastern Anatolia	51	179	31	51	190	31
South-East Anatolia	47	175	31	46	188	35
Mediterranean	46	161	35	45	183	39
Turkey, total	554	189	42	543	196	39

SD- standard deviation

In the Turkish Heart Study which surveyed nearly 10,000 persons during the years 1990-93 in and around 6 Turkish cities, following total cholesterol mean values were obtained for men and women, respectively (7): Istanbul 202, 181 mg/dl; Adana 184, 190 mg/dl; Trabzon 174, 175 mg/dl; Kayseri 171, 179 mg/dl; Aydın 173, 166 and Ayvalık 160, 162 mg/dl.

When only the age group of 40-59 years was considered in the stated towns, mean levels in men were 198, and in women-188 mg/dl. Values in women were very close to those of the TEKHARF study, while the excess of 13 mg/dl among men, is likely to originate from selection of the cohort mostly from factory workers and executives in the Turkish Heart Study.

Regional differences in serum total cholesterol were noted to diminish in the TEKHARF 2002 survey (9). With reference to the Mediterranean and Black Sea regions having the lowest levels, the regions of Marmara ($p<0.001$) and Central Anatolia ($p<0.05$) had significantly higher total cholesterol values. Differences in men and women were reduced to 11 to 14 mg/dl, respectively.

Hypercholesterolemia

In exactly 1/4 of adults in 1990, reflecting 7.5 million of the population at the time, hypercholesterolemia of ≥200 mg/dl was estimated to be present. Concentrations >300 mg/dl suggesting the presence of familial hypercholesterolemia were encountered in 7 per mille –representing 200-210,000 people nationwide. The prevalences by age groups of hypercholesterolemia ≥200 mg/dl in the 2000 survey is depicted in the Figure 2. In individuals of 30 years or over, levels exceeding the stated limit were observed in 28% of men and 35% of women.

In the Turkish Heart Study, hypercholesterolemic levels of ≥200 mg/dl were recorded in 32% of men and 22% of women. These proportions may be compared to prevalence of 48% of men and 50% of women aged 20-74 years in the U.S. (8), implying that related prevalence among Turkish adults existed in no more than half that of US adults.

Stability in Cholesterol Levels Over Time

When standardized for the age bracket 30-79 years, participants in the survey 2000 failed to show significant mean changes of total cholesterol levels, with 180.2 and 186.8 mg/dl in men and women, respectively, compared to those of 10 years previously (10). Also in the survey of 2001/02 (including the newly enrolled cohort) mean cholesterol concentrations among men and women were found to be 186 and 195 mg/dl, respectively. Consequently, as contrasted to the rising triglyceride levels, total cholesterol values may be regarded as stable in the mentioned period extending to over a decade.

The effect of family income on levels of total cholesterol had been examined in both the TEKHARF (2) and the Turkish Heart (7) studies and similar findings elicited, namely the better the family income, (ironically) the higher were the total cholesterol levels. This trend was the reverse observed in Western populations in which significant improvements in cholesterol values were noted with higher socioeconomic status.

Triglyceride Levels

Changes in plasma triglyceride concentrations have been the most conspicuous among those of cardiovascular risk variables in the past 12 years in Turkish adults. As elsewhere, triglyceride values displayed in our participants not a normal, but rather a log normal distribution. Median values in the 1990 survey by age groups provided in the Figure 3 make clear that a plateau of 137 mg/dl was attained in men aged 35-55 years followed by a declining trend, whereas in women a continuous rise was observed to reach levels of 140 mg/dl at the age group of 60-69 years. Mean values, at ages standardized to 30-69 years, were 149 in men and 126 mg/dl among women (2). Overall mean triglyceride values in the Turkish Heart Study, which comprised a younger sample were 131 and 105 mg/dl, in men and women, respectively.

In urban participants, triglyceride values exhibited in men and women only 8 and 4 mg/dl higher values than in rural ones, differences that were not significant.

Hypertriglyceridemia

The normal triglyceride limit for metabolic syndrome defined by the recent NCEP ATP III guidelines as <150 mg/dl, better suited for Turks, will be used. As seen in the Figure 4, 39.6% of Turkish men and 29.2% of women display hypertriglyceridemia. This corresponds to approximately 6.7 million men and 4.9 million women, a total of 11.6 million adults aged 30 years or over who possess triglyceride levels ≥150 mg/dl. Further of note is that 43% of Turkish adults have triglyceride values in the range between 100 and 200 mg/dl.

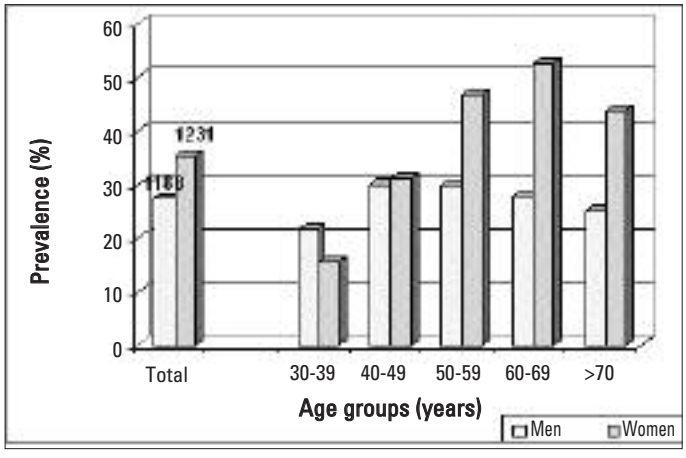


Figure 2. Prevalence of hypercholesterolemia (≥200 mg/dl) in men and women of various age groups, in year 2000

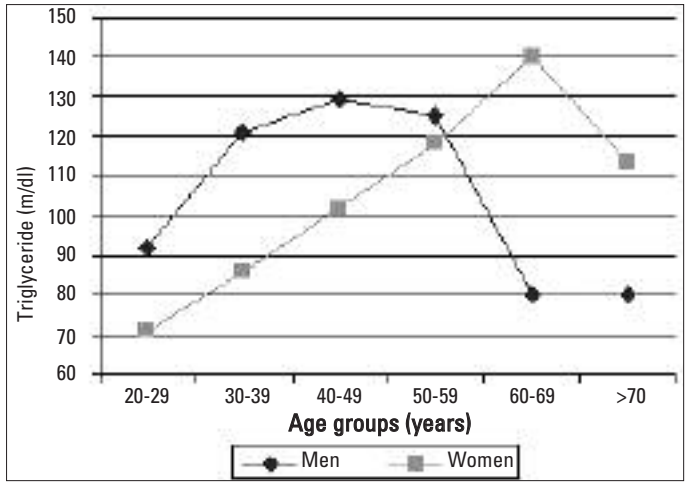


Figure 3. Median fasting plasma triglyceride values in Turkish men and women in year 1990

Major Rise in Triglyceride Levels Over Time

The course of mean fasting plasma triglyceride levels by age groups in the past 10 years is depicted graphically in the Figure 5. As indicated by weighted average values, men in 1990 who harboured triglycerides of 147.7 mg/dl recorded an increase of 4 mg/dl after age-adjustment. Women experienced even a much higher rise, namely 12.8 mg/dl from a mean of 122.6 mg/dl to 135.4 mg/dl in year 2000. These differences are more pronounced in the certain age groups. Tendency to a rise persisted in the survey 2001/02. This observation represents an average annual increase by 1 mg/dl in plasma triglycerides in Turkish adults, age being kept constant (10), and constitutes – along with the augmentation of (abdominal) obesity – the two salient changes since 1990 in the risk factor profile in Turkish adults. A similar increase was confirmed on a limited number of subjects by Mahley and associates (12).

Variation in regional triglyceride levels: In the survey 2001/02 plasma triglycerides were the lowest in women and men of the Marmara region (127 and 160 mg/dl, respectively). By contrast, residents of the Mediterranean region (172 and 195 mg/dl) and women of the Southeast (160 mg/dl) and Central Anatolia (145 mg/dl) had significantly higher triglyceride levels (11).

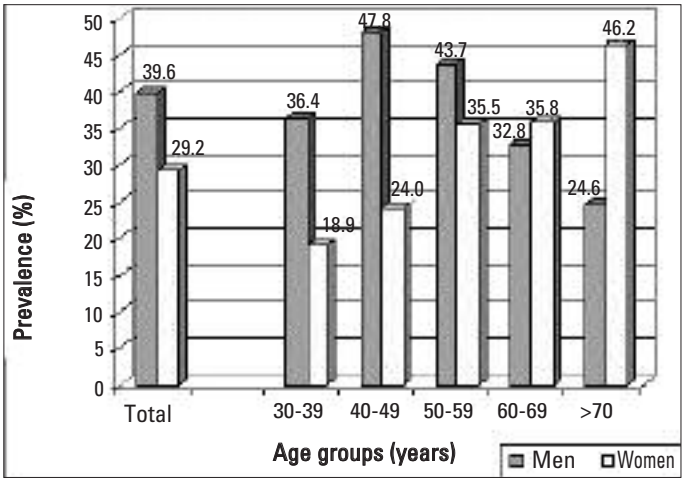


Figure 4. Prevalence of hypertriglyceridemia (≥150 mg/dl) in Turkish men and women of various age groups, in year 2000

High Density Lipoprotein Cholesterol (HDL-Cholesterol; HDL-C)

Concentrations of this parameter have been first measured in the TEKHARF study from the survey 1997/98 onwards. In the Turkish Heart Study had been reported a few years previously that mean HDL-cholesterol, concentrations in 2119 men were 38.3 mg/dl, and in 527 women 45.5 mg/dl (12). No significant difference existed with aging. The same group of investigators found later even lower levels of HDL-cholesterol in 405 adults (12).

The TEKHARF survey of 1997/98 confirmed these data with HDL-cholesterol levels averaging 37.2 mg/dl in 1211 men and 44.9 mg/dl 1261 women (13) (Table 3). Levels increased significantly with age in women alone ($r = 0.14$, $p < 0.001$). They did so also in men 4 years later so that a rise by 1 to 1.5 mg/dl per decade of age was noted in both genders (14).

Thus HDL-cholesterol levels encountered in Turks are lower by 20% than in Americans and Germans in either gender (15).

Prevalence of Low HDL-Cholesterol Levels

Lower concentrations than <40 mg/dl had been encountered in the Turkish Heart Study in 74% of men and 53% of women (12). The TEKHARF cohort of 2001/02 revealed similar though slightly lower prevalence, namely in 64% and 35.5%, respectively; 69% of women exhibited levels lower than 50 mg/dl recommended as low by the NCEP in 2001 (14). When the proportions in the study with higher representative power is taken into account, nearly 23 million adults with low HDL-cholesterol levels may be currently estimated to exist in Turkey. This is a very high prevalence.

Determinants of HDL-Cholesterol Values

In our cohort of 2326 persons, multiple linear regression analysis was made which included other than age, cigarette smoking, waist circumference, physical inactivity, serum concentrations of fasting insulin and C-reaktive protein (CRP), all known to be associated with decline in HDL-cholesterol. In the Table 4 it is summarized that, after age adjustment, all 5 variables were associated with a decrease in HDL-C. A doubling in insulin concentrations was associated with a 20% reduction of HDL-C values and a doubling of CRP with a 10% reduction of HDL. In men using alcoholic drinks once per week or more often, a rise by 1.4 mg of HDL-C was associated, compared to the remainder of men.

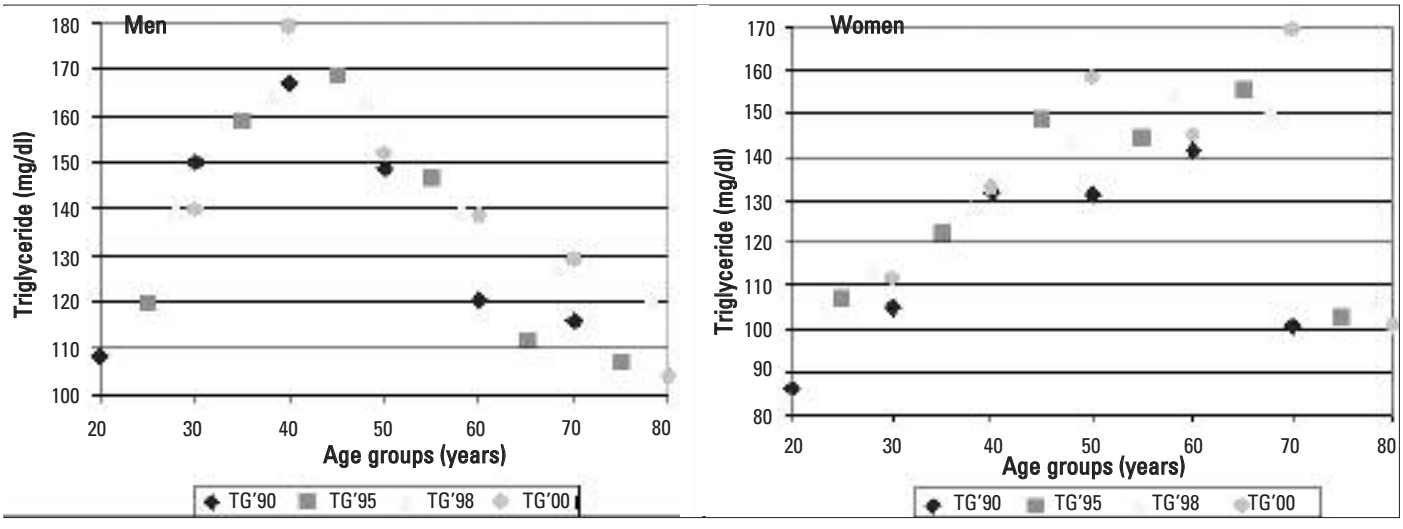


Figure 5. Course over time of mean triglyceride (TG) concentrations in Turkish men and women, 1990-2000

When triglycerides, apolipoprotein AI and B concentrations were added to the linear regression model, the number of individuals were reduced to 578. Analysis for the sex- and age-adjusted association with HDL-C was examined in this model with smoking, alcohol intake, grade of physical activity and household income, a direct association was noted with the latter and apo AI, total cholesterol and alcohol use, while an inverse one existed between HDL-C and apo B, triglyceride, waist circumference and smoking; whereby all associations had a p<0.001, except for alcohol which was borderline significant. Following increments, corresponding to 1 standard deviation, were associated with following changes in HDL-C. For 80 mg/dl triglycerides 1.6 mg reduction in HDL-C, for 12 cm waist girth 1.33 mg/dl reduction in HDL-C, for being current smoker 3.16 mg/dl reduction in HDL-C, for 30 mg/dl of apo B 2.07 mg/dl reduction in HDL-C, for 40 mg/dl of total cholesterol an increase of HDL-C by 3.32 mg/dl. Alcohol usage once a week or more often was associated with an elevation of HDL-C value by 3.5 mg/dl compared to the remaining individuals.

Following conclusions may thus be reached with respect to the Turkish community: cigarette smoking, abstinence from alcohol usage, high levels of triglycerides and apo B, an increase in waist circumference and insulin concentrations and, in men physical inactivity, are independent determinants of low HDL-cholesterol values. Associated with low HDL-cholesterol is an independent increase in the proinflammatory marker. In addition, significant genetic determinants exist which lead to hyperinsulinism, abdominal obesity, hypertriglyceridemia that affect HDL-C directly or via an insulin resistance. It has been estimated that genetic factors explain 40-80% of the variance of serum HDL-C (16-18).

Mahley and coworkers have observed that hepatic lipase activity in Turks is elevated by approximately 25-30% that may contribute to the low HDL-cholesterol levels (19) and that reductions in HDL-cholesterol of up to 10-20 mg/dl in girls and boys occur during adolescence which they considered to be due to a hormonal imbalance (20).

Table 3. Mean HDL-cholesterol values

	Men			Women		
1998 age	n	mean	SD	n	mean	SD
≥70 years	87	42	14	72	46.5	11
60-69 years	199	39.2	13	214	49	15
50-59 years	233	37.4	11	252	44.8	11
40-49 years	319	36.3	12	337	44.4	13
30-39 years	346	35.6	11	352	42.7	12
27-29 years	27	35.4	10	34	44.2	13
	1211	37.2	11.7	1261	44.9	12.8

HDL: high density lipoprotein, SD: standart deviation

Table 4. Independent determinants of age - adjusted HDL-cholesterol by linear regression analysis in the TEKHARF cohort (n= 2326)

	b	%95 confidence interval	p
Smoking	-1.55	-1.87; -1.23	0.000
Waist (cm) (n= 2137)	-0.14	-0.18; -0.105	0.000
Log insulin (n= 1217)	-5.90	-7.75; -4.06	0.000
Log CRP (n= 1888)	-2.65	-4.1; -1.6	0.000
Alcohol consumption (>1 vs <1 per week)(n=1108**)	1.38	0.71; 2.04	0.000
Degree of physical activity* (1169 women)	1.17	0.05; 2.29	0.040

*nonsignificant in men, **only men
CRP: C-reactive protein, HDL-high density lipoprotein

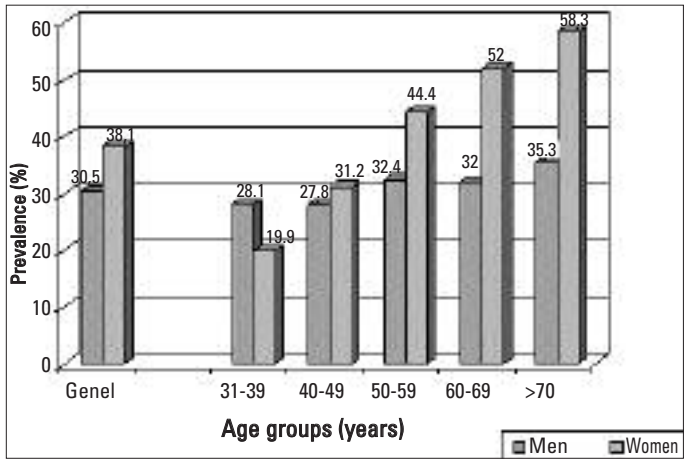
Low Density Lipoprotein Cholesterol (LDH-Cholesterol, LDH-C)

Mean LDL-cholesterol, concentrations in the Turkish Heart Study among 2119 men were 136 mg/dl, and among 527 women-111 mg/dl (12). Above age 40, mean values rose to 148 and 142 mg/dl, respectively. Low density lipoprotein-cholesterol levels that are derived from HDL-cholesterol values could be calculated in the TEKHARF study from the 1997/98 survey onwards; these failed to show significant changes in the subsequent years. In the 2001/02 survey, mean values in 842 men were 114.6 ±34.7 mg/dl, and in 999 women-122.4 ±38 mg/dl (unpublished observations). Noteworthy is that the Turkish Heart study, not having a representative sample, reported high LDL-cholesterol levels in men (though not in women). Mean values in women above the age 30 years have been consistently higher in our experience than men levels were directly correlated with age, slightly in men (r =0.11, p<0.004), more pronouncedly in women (r =0.27, p<0.001) (21).

Low density lipoprotein-cholesterol levels in our adults are lower in both genders by about 30 mg/dl than their American or Danish counterparts (15,22,23).

Prevalence of High LDL-Cholesterolemia: Borderline-high and high values of LDL-cholesterol (≥130 mg/dl) were noted in the Turkish Heart study in 37% of men, and 28% of women (7). In the TEKHARF 2001/02 cohort, the distribution in age groups being illustrated in Fig. 6, similar prevalences were elicited though in reverse proportions: in 31% of men, and 38% of women (unpublished observations). In half of female and 60% of male Turkish coronary patients, LDL-cholesterol concentrations have been estimated to be normal (<130 mg/dl) (24). This finding should underline for our physicians that, the development of CHD with normal LDL levels may be encountered commonly in our society.

Correlates of LDL-cholesterol: The strongest correlates in the TEKHARF sample have obviously been total cholesterol (r =0.86) and apolipoprotein B (r =0.65); in addition, triglycerides (r =0.14 and 0.28 in men and women), waist circumference (r =0.15) and CRP (r =0.15) concentrations have disclosed significant but moderate correlations with LDL-cholesterol.



LDL- low density lipoprotein

Figure 6. Prevalence of LDL-cholesterolemia ≥130 mg/dl in adults (survey 2001/02)

Total Cholesterol/HDL-Cholesterol Ratio (TC/HDL-C)

In individuals having LDL-cholesterol values within normal limits, coronary disease risk may vary between high and low depending on the HDL-cholesterol concentration. Two ratios may be resorted to evaluate risk in such persons: a) the lipoprotein ratio (LDL-C/HDL-C), b) the TC/HDL-C ratio. The latter ratio which also comprises very low density lipoprotein (VLDL) is used more commonly and predicts risk more accurately, especially in populations such as our's having high levels of triglycerides and a high prevalence of metabolic syndrome. Since ratios exhibit log-normal rather than normal distribution, median values rather than mean values are used in assessing correlations with other variables.

Median TC/HDL-C ratio in the 30-69 age bracket, have been reported to be among Germans 4.6 and 3.5 (25), Americans 4.5 ve 3.8 (8) in men and women, respectively, while being nearly 0.6 units higher among Turks, namely 5.18 and 4.25 (15). When patients with coronary heart disease are considered, median TC/HDL-C values amounted to 5.17 and 5.05, respectively (24). In the TEKHARF cohort of 2001/02 exactly one-quarter of men exhibited >6.0 units, 37% a ratio over 5.5, generally considered to be high-risk. In the same survey in which women disclosed a median cholesterol ratio of 4.4, 32% had a ratio ≥5.0. Since the mean ratios in the Turkish Heart Study were 5.4 in men and 3.9 in women (12), they were in essential agreement, except for being slightly lower in women.

Dyslipidemia and its Relation to Abdominal Obesity

We recently studied the extent of visceral adipose tissue (VAT) area by computer tomography (CT) in 157 men and women of the Istanbul residents of the TEKHARF study cohort, and attempted to discern the relationship between VAT and dyslipidemia and certain other atherogenic risk factors on the one hand and CHD diagnosis on the other (26). Apolipoprotein B and HDL-cholesterol in men, and HDL-cholesterol in women were independently associated with VAT area in linear regression models that also comprised triglycerides, fasting insulin and CRP concentrations. In the study sample comprising 13 individuals with a CHD diagnosis, the age-adjusted odds ratio (OR) of cutpoints of VAT area > vs. <140 cm2 in men and > vs. <120 cm2 in women was 11.3 (95%CI 1.37; 93).

Serum Total Phospholipids

In the 2003 screening of the Turkish Adult Risk Factor Study, phospholipids were measured firstly in 452 men and women in the Marmara and Central Anatolian regions (27). A method that measures the total phosphatidylcholine, sphingomyelin and lyso-phosphatidylcholine was used. Serum total phospholipid levels were significantly different between men (192.2 ±32.0 mg/dl) and women (204.9 ±41.2 mg/d). Multiple linear regression analysis among 13 risk parameters revealed triglycerides, LDL-C, HDL-C, and complement C3 as independent significant determinants of phospholipid levels. Sex- and age-adjusted OR of phospholipid levels was not found to be significant for prevalent coronary heart disease. Age-adjusted OR of phospholipid levels for metabolic syndrome was significant in men with an OR 1.013.

Apolipoproteins A-I, A-II, B and C-III

The macromolecular lipoproteins, aside containing a core of cholesteryl esters and triglycerides, contain an outer shell of phospholipids and specific protein components, the apolipoproteins (apo). Apo A is the chief component of HDL, while apo B is found in VLDL, LDL, chylomicrons and lipoprotein(a). Apolipoproteins, being synthesized in the liver and intestinal mucosa, help to solubilize plasma lipids such as cholesterol, cholesteryl ester and triglycerides and thus provide their transport. The surface of lipoprotein particles formed by protein components has important functions in lipid metabolism, since it interacts with enzymes and lipid transfer proteins cleaving triglycerides or esterifying cholesterol, as well as with receptors located on the cell surface. Apo A-I is antiatherogenic, whereas apo B is atherogenic.

In the TEKHARF study, serum apo A-I and apo B measurements were made initially in the field using Behring kits and an immunoturbidimetric method, but in the last two years in a central laboratory nephelometrically. Mean apo B values assayed in 1465 subjects in the cohort 2001/02 were 114.6 ±46 mg/dl and 114.1 ±46 mg/dl in men and women, respectively. Table 5 summarizes the distribution by age groups of apoproteins along with triglycerides, LDL-C and CRP. Apo B values tend to rise with age ($r = 0.10$, $p < 0.001$), contrasted to those of apo A-I that are not significantly affected.

Correlations of apo B concentrations assayed in 1200 men and women, with certain lipid and non-lipid variables are shown in Table 6. Strong correlations were obtained particularly with plasma triglycerides and LDL-cholesterol (r =0.43 and 0.36), moderate but highly significant ones with fasting insulin, indices of (abdominal) obesity, log CRP and physical inactivity. No significant correlation was found between cigarette smoking and either apo B or apo A-I; nor between other parameters and apo A-I values. This observation casts some doubt on the reliability of our apo A-I assays.

Apolipoproteins are measured primarily for assessing the cardiovascular risk; furthermore, they are useful evaluating the therapeutic efficacy (i.e. with respect to risk for development of restenosis). In laboratories standardized for the Center for Disease Control, a ratio of apo A-I/apo B lower than 1.2, clearly signifies increase in vascular risk. Normal limits are provided for apo A-I as 110-160 mg/dl, for apo B 70-130 mg/dl (28) (50-90 mg/dl according to CDC standards).

Concentrations of Apo A-II, the second major apolipoprotein of HDL, have been measured in the TEKHARF study only in the 2003 survey in selected 194 men and women (29). Highly significant correlations existed between apo A-II and phospholipids, apo A-I, HDL-C, total cholesterol (r=0.66 to 0.30), triglycerides, complement C3, LDL-C, body mass index, (inversely) smoking and age (r=0.26 to 0.15). A borderline inverse association was noted between apo A-II and metabolic syndrome. Complement C3 and HDL-C emerged as the only independent determinants of apo A-II levels among 12 parameters in a multivariate linear regression analysis. Sex- and age-adjusted apo A-II did not prove to be significant for CHD, nor for metabolic syndrome or diabetes in logistic regression analysis.

Apo B values >120 mg/dl, also a marker of high vascular risk, were observed in our cohort in 34% of men (=201/593), and 33% of women (=203/614).

Low apo A-I levels (<110 mg/dl) were encountered in our cohort in 30% of men (=134/444) and 18% of women (=80/455).

Another marker of high coronary risk, a ratio of apo A-I/apo B <1.2 was noted in 54% of our male (=241/444) and 40% of the female cohort (=180/455).

It has been pointed out that in clinical evaluation the conventional cholesterol model has substantial limitations, 3 measurements and one calculation (for LDL-C) being required in this context, and that analyses have to be carried out in fasting blood (30). Apo B has been shown in multiple studies to have a higher predictive value as marker of vascular risk than any index of cholesterol. Fasting is not required for apo B. It is known that each cholesterol-carrying lipoprotein particle contains one apo B molecule. Therefore, plasma apo B level reflects the total number of atherogenic particles. Moreover, it has been stressed that the formula to calculate LDL-cholesterol is inaccurate in type 2 diabetics (31). In the diagnosis and management of men and women (such as Turkish adults) with dyslipidemia but harbouring normal or low LDL-cholesterol concentrations, the opinion is shared by many workers in the field that apo B and apo A-I levels are more valuable than the cholesterol model (30).

Hypertriglyceridemia with Elevated Apo B (hyperTg hyperapoB)

Several cross-sectional and two prospective studies (32,33) in hypertriglyceridemic subjects, in which small, dense LDL are the rule, have shown that risk is greater in hyperTg hyperapoB than in hyperTg normoapoB reflecting the importance of LDL particle number. We have recently tested this hypothesis in the TEKHARF study in three groups of postmenopausal obese women: normolipidemic with normal apo B; hyperTg with normal apoB; and hyperTg hyperapoB (34). Complement C3, fasting insulin and glucose were significantly higher and HDL-cholesterol and sex hormone-binding globulin levels significantly lower in the hyperTg hyperapoB group than in group 1. The mean risk score in group 3 and the odds ratio for coronary disease by logistic regression analysis were significantly higher, 2.56 (CI 1.12-5.85, p=0.026), compared to the two other groups combined. In examining the whole group, apo B levels correlated significantly with a wider array of proatherogenic risk factors than did LDL-cholesterol, particularly being linked to C3 and glucose as well as the risk score.

Apolipoprotein C-III

Plasma apolipoprotein C-III (apoC-III), a major component of triglyceride-rich lipoproteins (TRL) and a minor component of HDL, is a reliable marker of TRL metabolism which reflects cardiovascular risk (35). ApoC-III inhibits the ligand for TRL receptor to lipoprotein lipase (LPL) and hepatic triglyceride lipase (35), and the ensuing delay in postprandial clearance of TRL has been related to elevated CHD risk (36). As far as can be assessed, apoC-III in VLDL and LDL, rather than in LDL has been predictive of the likelihood of coronary risk (37).

In the course of the 2001 survey of the TEKHARF study confined to the Marmara and Central Anatolian regions, blood was sampled in 857 unselected men and women for apoC-III and measured by turbidimetric immunoassay method in the Institute for Clinical Chemistry and Laboratory Medicine of the Münster University, Germany (38). Levels of nonHDL apoC-III >7.0 mg/dl indicated the presence of metabolic syndrome with an odds ratio of 4.7 (38). Total apoC-III and nonHDL apoC-III were associated with prevalent CHD in men, even after adjustment for age, LDL- and HDL-cholesterol (p <0.05 and p <0.002): the OR between the upper and lower quartiles proved to be 3.88 (CI 1.3; 11.4), and 8.8 (CI 2.6; 29.8), respectively (Fig. 7). The capacity of total and nonHDL apoC-III to determine the metabolic syndrome is likely

Table 5. Distribution of mean apo A-I and apo B levels according with age groups (together with triglycerides, LDL-C and CRP)

Age groups (years)	n	ApoAI mg/dl	ApoB mg/dl	SD	Triglycerids, mg/dl	LDL-C, mg/dl	CRP, mg/L
Men							
31-39	89	117.2	110.7	43	201	107.9	2.19
40-49	241	124.3	112.7	36	195.6	111.2	4.15
50-59	171	127.4	118	42	181.8	116.3	3.57
60-69	126	125.9	112.1	43	157.1	113.6	6.38
>70	78	121.5	116.6	76	141.6	117.5	6.13
Turkey, total	705	124.2	114.1	46	179.7	113.3	4.38
Women							
31-39	94	127	102.6	43	118.6	105.5	2.22
40-49	257	136.4	106	38	138.7	118.2	3.05
50-59	183	138.2	119.9	48	155.1	126.8	4.33
60-69	147	142.5	124.4	49	169.6	135.2	5.75
>70	79	133.6	126.7	54	146.5	137.3	4.64
Turkey, total	760	136.6	114.6	46	146.8	123.6	3.95

apo: apolipoprotein, CRP: C-reactive protein, LDH-C: low density lipoprotein cholesterol

Table 6. Correlation of apolipoprotein B concentrations, measured in 1200 men and women, with some lipid and non-lipid variables

Men-Women together	Apolipoprotein B		
	n	r	p
Age	1207	0.099	0.001
Waist	1198	0.156	0.000
Body mass index	1157	0.133	0.000
log C-reactive protein*	1134	0.141	0.000
Triglycerides*	997	0.432	0.000
Low density cholesterol	621	0.364	0.000
Log insulin*	719	0.135	0.000
Smoking*	591		AD
Physical activity*	1159	-0.091	0.002

related to their being a good marker of TRL metabolism and to their inhibiting the LPL (35).

Lipoprotein(a) [Lp(a)]

Lp(a) concentrations were determined nephelometrically in a sample of 214 elderly subjects in the TEKHARF study (39). Geometric mean values were 9.6 ±2.8 mg/dl in men and 12.1 ±3 mg/dl in women (p<0.001). In conformity with the knowledge that the variance of Lp(a) is overwhelmingly related to apo(a) isoforms, values were not correlated with any of 15 risk parameters except in men positively with LDL-cholesterol, inversely with waist circumference and body mass index, and interestingly, with fasting insulin (r =-0.36, p=0.002). The diagnosis of metabolic syndrome tended to be inversely correlated with Lp(a) in men.

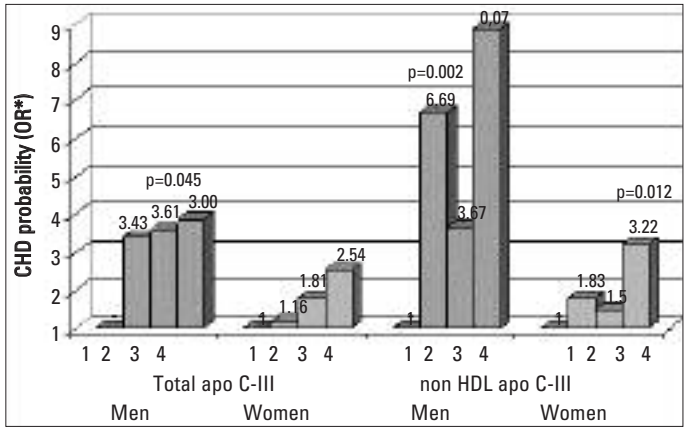
Lp(a) concentrations had been determined in Turkish samples in 4 previous studies using the ELISA method. In 800 men and women in the Turkish Heart Study, mean values were reported to range between 11.2 and 14.7 mg/dl (7). Somewhat higher levels were found in the regional studies (40-42).

Prediction of CHD Risk by Lipoproteins

Prospective analyses of variables for the prediction of fatal and nonfatal CHD in the TEKHARF study, after exclusion of participants with a diagnosis of CHD at baseline, have been performed by multiple regression with respect to two periods. Analyses pertain to the 10-year period 1990-2000 and to the 4-year period between 1997/98 and 2001/02 – which incorporated also risk factors such as HDL-cholesterol and waist circumference.

Independent Predictors of Coronary Mortality and Morbidity

A logistic regression model was analyzed of 11 salient risk factors in 1990 for the prediction of subsequent fatal and nonfatal CHD. Age, systolic and diastolic pressures, total cholesterol, HDL-C, total/HDL-cholesterol ratio, body mass index, presence of diabetes, smoking status, physical activity grade, family income were included in the model. Among 1397 subjects with no missing data, CHD had been diagnosed in 122 persons (64 males). Values of 1990 were used for most parameters, except for diabetes for which a diagnosis at baseline as well as in the course of follow-up, was utilized and for HDL-cholesterol for which the first measurements in 1997 were utilized. Findings summarized in the Table 7 indicate that, apart from age, 4 independent significant predictors of future CHD events were systolic BP, total/HDL-cholesterol ratio, presence of diabetes and smoking status (10,15). In addition, body mass index was an independent predictor in men alone: each increment of 4 kg/m2 raised the coronary risk by 40%. Of the two foremost modifiable predictors of CHD events among Turkish adults, a 20-mmHg increment in systolic BP raised the risk of CHD events by 52%, and an increment of 2 units in the total/HDL-cholesterol ratio by 68%.



apo: apolipoprotein, CHD: coronary heart disease, HDL: high density lipoprotein, OR: odds ratio

Figure 7. Prospectively evaluated relative risk for CHD of quartiles of total and non-HDL apo C-III in men and women (adapted from Ref. 39)

Predictivity of Risk Factors in the 4-Year Period

Since in our study waist circumference and HDL-cholesterol measurements started from the 1997/98 survey on, values at this baseline were analyzed multivariately for the subsequent 4-years' follow-up. In a logistic regression analysis comprising 11 variables [age, sex, systolic and diastolic BP, waist circumference, body mass index, smoking status (smokers, nonsmokers), total cholesterol, HDL-cholesterol, presence of diabetes and physical activity grade], age, smoking status and diabetes were significant predictors in both genders (Table 8). Further significant predictors were HDL-cholesterol among women, and systolic BP and total cholesterol in men, while waist circumference was of borderline significance in men (14).

In this analysis, an increment of 40 mg/dl in total cholesterol, equivalent to 1 standard deviation (hazard ratio), was associated with a rise in CHD risk by 68%, independent of the other factors (14).

The relative risk (RR) of HDL-C, independent of 10 other risk factors, was in men 0.971 (p<0.02), and in women 0.980 (borderline significance) (14). When both genders were combined, RR proved to be 0.975 (p<0.002), which implies that a decrement of 12 mg/dl in HDL-C (=1 hazard ratio) was associated with a rise by 36% in nonfatal and fatal CHD events.

Age-Adjusted CHD Likelihood in Cross-Sectional Evaluation

Triglycerides: In a total of 1736 fasting participants in the 1997/98 cohort, plasma triglycerides had been measured with the Reflotron apparatus. Definite or suspected CHD was diagnosed in 122 subjects. Age and HDL-cholesterol as potential confounders of the relationship between triglycerides and CHD were included in a regression model, triglyceride levels in men and women were classified into 4 categories (43). The major finding regarding levels of plasma triglycerides to reflect atherogenicity was not the highest category, but rather the mid-high category, namely men and women in the 140-212 mg/dl brackets. Compared to the lowest quartile, this quartile disclosed a significant odds ratio for CHD risk of 1.42 (p <0.045), after adjustment for age, LDL-C, HDL-C, body mass index and smoking, in other words, this level of "hypertriglyceridemia" in Turks indepen-

Table 7. Independent predictors (for the year 1990) of coronary mortality and morbidity, developed diuring 10 years of the TEKHARF study,

Men and women *n= 1397*			
Variable	**p**	**Exp _**	**%95 CI**
Age (year)	0.000	1.049	1.030; 1.069
Systolic pressure (mmHg)	0.003	1.021	1.007; 1.035
Total/HDL-cholesterol	0.006	1.296	1.076; 1.560
Presence of diabetes ('90-'00)	0.02	1.429	1.058; 1.930
Ex smokers vs. nonsmokers	0.014	1.703	

At the begining model also included total cholesterol, HDL-C, diastolic pressure, physical activity and family income
Model included 122 persons with composite end point
CI: confidence interval, HDL: high density lipoprotein

dently added as much as 42% to the CHD likelihood (Fig. 8). The adjusted OR in women was stronger and in men weaker.

Apo B: The age-adjusted OR of serum apo B concentrations obtained in the 2001/02 survey for prevalent CHD was 1.007 (95%CI 1.001; 1.012). This implies that an increment of 40 mg/dl in apo B (=1 hazard ratio) is associated with an increase in CHD likelihood by 32%. The association was significant in women.

Comment for Risk Analyses

The observation that a 2-unit increment of TC/HDL-C adds an excess of 68% to both the nonfatal CHD risk and the combined CHD event risk, is in agreement with the experience in the Framingham (45,46) and PROCAM studies (25). Systolic pressure proved to be a stronger determinant of fatal rather than nonfatal CHD. When combined fatal and nonfatal CHD events are taken into account in our adults, the two best predictors appear to be systolic BP and the TC/HDL-C ratio. The latter has a greater role in women, while systolic pressure among men. Further independent predictors of CHD risk in men are body mass index and the status of a current smoker.

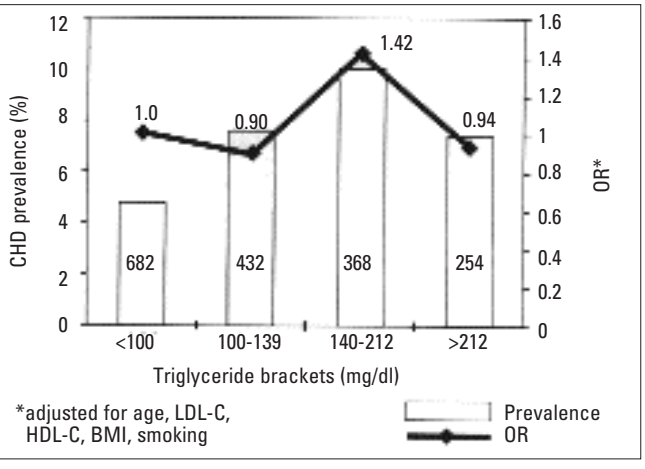
The similar magnitudes of the effect on CHD risk of TC/HDL-C ratio in populations with both high and low cholesterol levels likely originates from different mechanisms. The LDL-C level, the major constituent of the nominator of the ratio, is reflected in populations with high cholesterol levels by LDL particles which are primarily of type A. By contrast, the major factor among our adults, is the low HDL-C in the denominator of the ratio and the accompanying high levels of triglyceride-rich lipoproteins, in which instance the LDL particles are expected to be primarily of the small, dense type (type B).

Table 8. Independent predictors of CHD developed during 4 years of follow-up period in TEKHARF participants who was free of CHD in 1997/98 years

	p	Exp _	%95 CI
Men and Women n= 2269			
Age (years)	0.000	1.074	1.055; 1.094
Total cholesterol (mg/dl)	0.000	1.009	1.004; 1.014
Smokers vs. nonsmokers	0.001	2.043	1.324; 3.154
HDL-cholesterol (mg/dl)	0.002	0.975	0.959; 0.991
Presence of diabetes	0.004	2.008	1.244; 3.242
Systolic blood pressure (mmHg)	0.006	1.016	1.004; 1.027
Waist (cm)	0.045	1.025	1.001; 1.050

The following variables were also included into the logistic regression model: waist, diastolic blood pressure and the level of physical activity.
Model included 144 CHD patients (81 men, 63 women)

CI: confidence interval, CHD: coronary heart disease, HDL: high density lipoprotein



BMI: body mass index, CHD: coronary heart disease, HDL: high density lipoprotein, LDL: low density lipoprotein, OR: odds ratio

Figure 8. Triglyceride brackets and CHD likelihood among Turks. Graph shows that not the highest category, but rather the 140-212 mg/dl bracket confers significantly greater odds ratio, after adjustment for confounding factors (adapted from Ref. 43).

Impact of Lipid Profile on CHD Among Turks

Evidence is sufficiently strong that the best independent lipid predictor among Turks is –as outlined above- the TC/HDL-C ratio (10,15). In line with this opinion, the Turkish Society of Cardiology Guidelines on Prevention and Treatment of Coronary Heart Disease (47) utilized this as a strong risk variable in risk assessment; furthermore, Mahley and associates (12) recommended that lipid lowering treatment among Turks be based on TC/HDL-C ratio. In attempting to estimate the impact of our lipid profile on CHD, it may be appropriate to consider as high risk, TC/HDL-C ratios of ≥5.5 in men and ≥5 in women. Slightly more than one-third of Turkish adults, corresponding to 12 million adults, are included by these criteria, and based on the Framingham study data (48) that people with a TC/HDL-C ratio 5 to 5.5 exhibit a 10% CHD risk in the subsequent 10 years. Overall 120,000 citizens may be estimated to sustain a CHD annually for this reason. Via reducing the ratio by 1 unit in these people, the prevention of CHD in 35,000 persons each year may be anticipated.

The TC/HDL-C ratio is known to reflect the presence in plasma of LDL particles both of pattern A and pattern B. Since it is impractical to measure pattern B, i.e. small, dense LDL particles, overall in the population, it is generally held that such particles appear in plasma of individuals having triglycerides >130 mg/dl, and prevail in abundance at apo B levels exceeding 120 mg/dl (49). As small, dense LDL particles are rich not in cholesterol, but in triglycerides, their contribution to the values of total cholesterol is insufficient, but are nonetheless highly atherogenic. Therefore, in our population having low levels of HDL-cholesterol, it has been stressed that hundred-thousands of citizens harbouring total cholesterol concentrations in the 180-200 mg/dl range are at high risk, and the opinion has been expressed by us that the upper normal limit of total cholesterol be reduced to 180 mg/dl in Turks (23).

In conclusion, the lipid risk profile in Turkish adults is chiefly determined by low HDL-cholesterol and an excess of small, dense LDL particles which have underlying genetic causes as well as susceptibility to visceral adiposity. Consequently, tendency to the metabolic syndrome is strong and susceptibility to CHD is, regrettably, high as compared to many other populations. This constellation, I believe, emerged or became pronounced in the last few decades in our community and can largely be prevented, suffice it that related physicians and authorities regard this as a very serious public health issue and engage in appropriate effective preventive measures.

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