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Impaired protection against diabetes and coronary heart disease by high-density lipoproteins in Turks

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Abstract

The issue of whether or not incident type 2 diabetes mellitus and coronary heart disease (CHD) can be predicted by high-density lipoprotein (HDL) cholesterol in both sexes needs investigation. A representative sample of 3035 middle-aged Turkish adults free of CHD at baseline was studied with this purpose prospectively over a mean of 7.8 years. High-density lipoprotein cholesterol levels were found to be correlated in women positively with plasma fibrinogen and weakly with waist girth and C-reactive protein, and to be not correlated with fasting insulin. High-density lipoprotein cholesterol protected men against future CHD risk (for a 12-mg/dL increment: relative risk = 0.80 [95% confidence interval, 0.69-0.95]) after multivariable adjustment in logistic regression analyses for age, smoking status, physical activity grade, hypertension, abdominal obesity, diabetes, and lipid-lowering drugs. However, men were not protected against risk of diabetes. In women, HDL cholesterol was not associated with risk for CHD, whereas intermediate (40-60 mg/dL) compared with lower HDL cholesterol levels proved protective against risk of diabetes (relative risk = 0.57 [95% confidence interval, 0.36-0.90]) after adjustments that included apolipoprotein A-I tertiles. Yet higher serum concentrations failed to yield protection against diabetes. It was concluded that HDL particles confer partially lacking protection against cardiometabolic risk among Turks, and this impairment is modulated by sex. This highly important observation may result from a setting of prevailing chronic subclinical inflammation.

1. Introduction

For more than 30 years, high-density lipoprotein (HDL) particles have been known to be the mainstay of atheroprotective defense mechanisms of the human organism. In addition to the reverse cholesterol transport from the peripheral tissues, diverse mechanisms including antioxidant and anti-inflammatory functions have been demonstrated. High-density lipoproteins are able to inhibit the low-density lipoprotein (LDL) oxidation via paraoxonase [1] or apolipoprotein (apo) A-I and A-II [2]. High-density lipoproteins also inhibit cytokine-induced expression of endothelial cell adhesion proteins [3] and neutralize C-reactive protein (CRP) proinflammatory activity [4]. High-density lipoproteins further possess antithrombotic effects [5] and are able to inhibit apoptosis [6]. Each 1-mg/dL increase in HDL cholesterol level was estimated to be associated with a 2% to 3% decrease in the multiadjusted risk of coronary heart disease (CHD). However, atheroprotective activities may be deficient in type 2 diabetes mellitus, a process ascribed to (*a*) HDL enrichment with conformational alterations of apo A-I; (*b*) glycation of apolipoproteins and/or HDL-associated enzymes; and (*c*) oxidative modification of HDL lipids, apolipoproteins, and/or enzymes [7].

No part of this paper has been published or is under consideration for publication elsewhere. It complies with ethical considerations. All authors have participated in the study and approved the manuscript.

We do not consider that any potential conflict of interest of authors exists in regard to the study.

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In the past few years, besides failing to induce regression of atherosclerosis via raising HDL cholesterol levels by torcetrapib, a series of observations were reported suggesting that elevated HDL cholesterol may be associated with increased risk of CHD [8-10]. Several studies by Ansell et al [8] and Navab and associates [9] demonstrated in vitro that antioxidant enzymes can be inactivated in the presence of systemic inflammation and that HDL can accumulate oxidized lipids and proteins to turn them into a proinflammatory particle. More recently, in evaluating the significance for cardiovascular risk of HDL cholesterol levels, particle size, and apo A-I in 2 prospective studies, very high serum HDL cholesterol levels (>70 mg/dL) as well as highest categories of HDL particle size were found to be positively associated with cardiovascular risk [11]. High HDL cholesterol did not protect against coronary artery disease also when associated with combined cholesterol ester transfer protein and hepatic lipase gene variants [12].

Experimental and clinical evidence is thus accumulating that HDL cholesterol concentration does not reflect the totality of atheroprotective activities of HDL. Atheroprotective functions are affected, beyond diabetes, in conditions like CHD and chronic inflammation and through various interventions. High-density lipoprotein dysfunctionality has been ascribed to include advanced glycation and oxidation of HDL proteins and lipids, and changes in HDL composition and particle size [13].

Recent investigations of the ongoing population-based Turkish Adult Risk Factor Study produced evidence that increased levels of apo A-I concentrations were predictive of incident type 2 diabetes mellitus [14] and that circulating adiponectin was not protective of diabetes and hypertension in men [15] as it was in women. These findings may be considered to emerge in the setting of metabolic syndrome (MetS) highly prevailing among Turks [16]. We, therefore, evaluated prospectively the role of serum HDL cholesterol in protecting against incident CHD and new type 2 diabetes mellitus, whereby sex differences were specifically sought. Adjustment for cardiovascular risk factors, including serum apolipoproteins and CRP, and correlations of HDL cholesterol with certain inflammatory markers were used to identify the interrelationship of the findings.

2. Population and methods

2.1. Population sample

The Turkish Adult Risk Factor Study is a longitudinal population-based cohort study on cardiac disease and its risk factors in adults in Turkey carried out biennially in 59 communities in all geographical regions [17]. It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions, and rural-urban distribution [17]. Combined measurements of waist circumference and HDL cholesterol having been first made at the follow-up visit in 1997/1998, the latter examination formed the baseline. Participants, 28 years or older at baseline, were examined periodically up to the survey in 2007/2008. When individuals with prevalent CHD at baseline (n = 135) were excluded, the remaining 3035 participants free of CHD composed the cohort of the current study. Subjects numbering 147 with type 2 diabetes mellitus at baseline were excluded from the analyses only for incident diabetes. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Individuals of the cohort gave written consent for participation. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood, and recording of a resting 12-lead electrocardiogram.

2.2. Measurements of risk variables

Blood pressure (BP) was measured using a sphygmomanometer (Erka, Bad Tolz, Germany) after 10 minutes of rest while seated on the right arm, and the mean of 2 recordings at least 3 minutes apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00; Roche Diagnostics, Mannheim, Germany), with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index was computed as weight divided by height squared (in kilograms per square meter). Self-reported cigarette smoking was categorized into never smokers, former smokers (discontinuance of 3 months or more), and current smokers (regularly 1 or more cigarettes daily). Physical activity was graded by the participant himself into 4 categories of increasing order with the aid of a scheme [17].

Plasma concentrations of total and HDL cholesterol, fasting triglycerides, and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein cholesterol values were computed according to the Friedewald formula. In the final 4 surveys, the stated parameters, as well as insulin and CRP values, were assayed in a single central laboratory. Blood samples were shipped to Istanbul to be stored in deep freeze at −75°C until analyzed. Concentrations of insulin were determined by electrochemiluminescence immunoassay on Roche Elecsys 2010 (Roche Diagnostics). Serum concentrations of apo A-I and B and CRP were measured by the Behring nephelometry (Behring Diagnostics, Marburg, Germany). Plasma fibrinogen was assayed by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit. External quality control was performed with a reference laboratory in a random selection of 5% to 6% of participants. Data on baseline triglycerides, CRP, and insulin were available in 82%, 86%, and 57% of participants, respectively.

Table 1
Characteristics of sample population (N = 3035) at baseline, by sex

	n	Men, n = 1492		Women, n = 1543		P
		Mean	SD	Mean	SD	
Age (y)	3035	49.1	12.6	48.8	12.6	.41
Waist circumference (cm)	3035	94.2	11	90.4	12.5	<.001
Systolic BP (mm Hg)	3035	126.5	21.9	131.5	25	<.001
Diastolic BP (mm Hg)	3035	80.6	13	82.4	13.9	<.001
Body mass index (kg/m^2)	3035	26.4	4	28.8	5.6	<.001
Plasma fibrinogen (g/L)	2148	2.93	1.07	3.16	1.07	<.001
CRP[a] (mg/L)	2595	1.96	3.13	2.22	3.2	.006
Apo A-I (g/L)	1996	1.25	0.33	1.39	0.33	<.001
Apo B (g/L)	2066	1.14	0.36	1.13	0.36	.40
Fasting insulin[a] (mIU/L)	1732	7.62	2.12	7.75	1.93	.63
Total cholesterol (mg/dL)	3035	181	37.5	187.5	39.8	<.001
HDL cholesterol (mg/dL)	3035	37.5	11.5	47.5	12.8	<.001
LDL cholesterol (mg/dL)	2645	114	32	119	34	<.001
Fasting triglycerides (mg/dL)	2480	155	97.4	133.6	87.6	<.001
Fasting glucose (mg/dL)	2595	98.8	28.8	99.9	27	.38
Current/former smoker (n)	1220	805/297		289/56		<.001

[a] Mean ± SD denote values derived from log-transformed means and SD.

2.3. Definitions and outcomes

Hypertension was defined as a BP of at least 140 mm Hg and/or 90 mm Hg and/or use of antihypertensive medication. Individuals with type 2 diabetes mellitus were diagnosed with the criteria of the American Diabetes Association [18], namely, when plasma fasting glucose was at least 126 mg/dL (or 2-hour postprandial glucose >200 mg/dL) and/or the current use of diabetes medication. Individuals with abdominal obesity were identified using cut points of at least 95 cm in men [19] and at least 88 cm in women [20], as recently assessed in the Turkish Adult Risk Factor study.

Diagnosis of nonfatal CHD was based on the presence of angina pectoris, on a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardiogram [21], or on a history of myocardial revascularization. Typical angina and, in women, age at least 45 years were prerequisite for a diagnosis when angina was isolated. Electrocardiographic changes of "ischemic type" of greater than minor degree (codes 1.1-2, 4.1-2, 5.1-2, and 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively.

2.4. Data analysis

Descriptive parameters were shown as mean ± standard deviation (SD) and in percentages. Serum insulin and CRP, having skewed distribution of concentrations, were log-transformed for calculations. Two-sided *t* tests and Pearson χ^2 tests were used to analyze the differences between means and proportions of other groups. In predicting outcomes at baseline examination in multivariate analyses, estimates (and 95% confidence intervals [CIs]) for relative risk (RR) were obtained by use of logistic regression analysis in models that controlled for potential confounders. Relative risks for 1 SD of the log-transformed independent CRP were expressed in terms of a 3-fold increment. High-density lipoprotein cholesterol levels were analyzed as continuous variable or (with respect to diabetes) in 3 brackets (35-50 mg/dL in men, 40-60 mg/dL in women forming the intermediate bracket). The lowest category is congruent with limits widely used in regard to CHD risk; the highest category in women has been designated by the Adult Treatment Panel III as neutralizing 1 risk factor. Sex-specific apo A-I tertiles were formed by cutoffs of 112 and 135 mg/dL in men and 125 and 150 mg/dL in women. A value of *P* less than .05 on the 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Chicago, IL; no. 9026510).

3. Results

At baseline examination, 1492 men (mean age, 49.1 ± 12.6 years) and 1543 women (48.8 ± 12.6 years, *P* = .41) were available free of CHD (age range, 28-80 years). Metabolic syndrome prevailed in 39.9% of men and 40.7% of women. Mean follow-up constituted 7.8 years (total, 23 700 person-years). Coronary heart disease newly developed in 408 subjects (16.3 per 1000 persons per year), and incident type 2 diabetes mellitus developed in 325 individuals (13.8 per 1000 persons per year) when 147 cases of diabetes at baseline were excluded.

Baseline characteristics of the participants displayed relatively large waist girths with high serum triglyceride and low HDL cholesterol concentrations, whereas LDL cholesterol was not elevated (Table 1). Correlation of HDL cholesterol concentrations with other risk factors is shown in Table 2. These levels were significantly correlated in women

Table 2
Correlation of serum HDL cholesterol values with certain risk variables

	n	Men, n = 1492		Women, n = 1543	
		r	*P* =	*r*	*P* =
Age (y)	3035	0.13	<.001	0.12	<.001
Waist circumference (cm)	3035	−0.18	<.001	−0.09	<.001
Body mass index (kg/m^2)	3035	−0.21	<.001	−0.12	<.001
Fasting triglycerides (mg/dL)	2480	−0.21	<.001	−0.25	<.001
Fasting insulin[a] (mIU/L)*	1732	−0.10	.004	−0.03	.32
Apo A-I (mg/dL)*	1996	0.22	<.001	0.30	<.001
Apo B (mg/dL)*	1985	−0.11	.002	−0.08	.013
Total cholesterol (mg/dL)	3035	0.11	<.001	0.14	<.001
Fibrinogen (g/L)*	2148	0.06	.062	0.11	<.001
Smoking status (0-2)	3035	−0.04	.13	−0.02	.45
LDL cholesterol (mg/dL)*	2645	−0.04	.17	−0.06	.034
CRP[a] (mg/L)*	2595	−0.05	.08	−0.05	.048
Systolic BP (mm Hg)	3035	0.02	.46	0.01	.65
Diastolic BP (mm Hg)	3035	−0.03	.26	0.00	.93
Fasting glucose* (mg/dL)	2595	−0.02	.54	−0.00	.90

[a] Log-transformed.

positively with plasma fibrinogen and weakly with waist girth or CRP, and were not correlated with fasting insulin.

The association between HDL cholesterol levels and the 3 studied outcomes was each assessed in at least 2 multiple logistic regression models: first in a basic model encompassing the whole sample with adjustments for established risk factors such as smoking status, physical activity grade, hypertension, abdominal obesity, and diabetes; second by entering additionally CRP and/or apo A-I or B, which concomitantly reduced the encoded sample by one seventh to two fifths.

Table 3 indicates that HDL cholesterol concentrations significantly protected men against CHD (for a 12-mg/dL increment: RR = 0.80 [95% CI, 0.69-0.95]). In women, HDL cholesterol levels were not associated with incident CHD. This did not change substantially in models comprising CRP or fasting triglycerides and LDL cholesterol, except for minor attenuation in men. When HDL cholesterol was entered in 3 categories as stated in the "Population and methods" section in women, the intermediate and highest brackets were not different (RR = 1.04; P = .83 and .85, P = .58, respectively) from the lowest.

Because (in an analysis as in the following model 2) HDL cholesterol as a continuous variable was not significantly associated with incident diabetes in either sex (RR = 1.002, P = .8 in men; RR = 0.99, P = .16 in women), analysis by categories was undertaken. Table 4 demonstrates the association of 3 HDL cholesterol categories with the risk of diabetes in 3 models. In the basic model, adjustments were made for sex, age, smoking status, physical activity grade, abdominal obesity, hypertension, and use of lipid-lowering drugs. Apolipoprotein A-I tertiles were added in model 2, whereas CRP replaced abdominal obesity in model 3. The latter models included apo A-I for reasons described in the "Introduction" [14]. In men, in whom abdominal obesity was of paramount significance, no independent association emerged between increasing HDL cholesterol brackets and diabetes risk in any regression model. Intermediate HDL cholesterol levels in women (40-60 mg/dL) tended to be protective compared with lower levels in models 1 and 3 and proved so in model 2, irrespective of concomitant adjustment for abdominal obesity and other confounders (Fig. 1). Remarkably, the highest HDL cholesterol bracket in women did not confer significant protection. Inclusion of CRP levels in model 3 attenuated the independent protection in women by higher HDL cholesterol brackets.

Categorization using lowered cutoffs of 33 and 46 mg/dL in men and 40 and 56 mg/dL in women failed to reveal any essential change.

4. Discussion

Main findings in this prospective population-based study in which the protective role of HDL cholesterol was investigated included evidence in men of protection against CHD, but not against type 2 diabetes mellitus, and partial protection in women against diabetes, but not against CHD. This is the first documentation of impaired HDL protection

Table 3
Logistic regression analysis of certain risk factors for incident CHD, at baseline

	RR	95% CI	RR	95% CI	RR	95% CI
Model 1[a]	*Total, n = 408/3035*[b]		*Men, n = 221/1492*		*Women, n = 187/1543*	
HDL cholesterol (mg/dL)	0.991	0.982-1.001	**0.982**	0.97-0.996	1.000	0.99-1.01
Age (y)	**1.065**	1.054-1.076	**1.066**	1.05-1.08	**1.065**	1.05-1.08
Current smoking	**1.40**	1.05-1.89	**1.98**	1.32-2.97	0.87	0.51-1.47
Waist circumference (cm)	**1.026**	1.015-1.036	**1.031**	1.016-1.046	**1.020**	1.006-1.034
Hypertension (140/90 mm Hg)	**1.69**	1.30-2.21	**1.72**	1.15-2.59	**1.72**	1.20-2.45
Presence of diabetes	**2.43**	1.66-3.58	**1.90**	1.03-3.50	**2.80**	1.68-4.67
Model 2[a]	*Total, n = 365/2595*[b]		*Men, n = 198/1267*		*Women, n = 167/1328*	
HDL cholesterol (mg/dL)	0.993	0.983-1.003	**0.985**	0.97-1.000	1.001	0.99-1.015
Age (y)	**1.064**	1.05-1.08	**1.06**	1.05-1.08	**1.07**	1.05-1.09
Abdominal obesity (≥95/88 cm)	**1.69**	1.30-2.21	**1.99**	1.41-2.82	1.27	0.86-1.87
Hypertension (140/90 mm Hg)	**1.69**	1.28-2.24	**1.71**	1.11-2.63	**1.72**	1.18-2.50
Presence of diabetes	**2.43**	1.58-3.72	**2.05**	1.05-4.00	**2.82**	1.61-4.95
CRP[c]	**1.15**	1.08-1.23	**1.14**	1.03-1.25	**1.19**	1.08-1.33
Model 3	*Total, n = 319/2411*[b]		*Men, n = 172/1160*		*Women, n = 147/1251*	
HDL cholesterol (mg/dL)	0.995	0.984-1.006	*0.986*	0.97-1.002	1.004	0.988-1.019
Fasting triglyceride (mg/dL)	**1.002**	1.001-1.003	*1.002*	1.000-1.003	**1.003**	1.001-1.005
LDL cholesterol (mg/dL)	**1.009**	1.005-1.013	**1.011**	1.006-1.017	**1.007**	1.001-1.012

Model 3 = adjustments as in model 1 plus for triglycerides and LDL cholesterol. Encoded in model 1 were 60 and 87 with diabetes. Significant values are highlighted in bold.

[a] Adjusted also for sex (RR = 0.89, P = .42 in model 1; 0.64, P = .001 in model 2). Former smoking, physical activity grade, and use of lipid-lowering drugs were not significant.

[b] Number of new CHD/number at risk in model.

[c] Log-transformed values and expressed in terms of a 1-SD (3-fold) increment.

Table 4
Logistic regression analysis of certain risk factors for incident type 2 diabetes mellitus, at baseline

	RR	95% CI	RR	95% CI	RR	95% CI
Model 1[a]	*Total, n = 325/2888*[b]		*Men, n = 168/1432*		*Women, n = 157/1456*	
HDL cholesterol (35-50/40-60)	0.89	0.69-1.15	1.03	0.72-1.47	0.79	0.54-1.14
HDL cholesterol (≥50/60 mg/dL)	1.04	0.71-1.53	1.08	0.62-1.88	1.01	0.58-1.75
Current smoking	0.81	0.59-1.10	0.84	0.56-1.26	0.81	0.49-1.35
Physical activity (I-IV)	**0.87**	0.76-0.999	0.91	0.77-1.08	*0.79*	0.61-1.01
Abdominal obesity (≥95/88 cm)	**2.94**	2.22-3.88	**2.74**	1.89-3.96	**3.25**	2.11-5.00
Hypertension (140/90 mm Hg)	*1.35*	0.99-1.82	1.09	0.67-1.80	**1.60**	1.07-2.37
Model 2[a]	*Total, n = 234/1893*[b]		*Men, n = 118/931*		*Women, n = 116/962*	
HDL cholesterol (35-50/40-60)	**0.72**	0.53-0.99	0.95	0.60-1.50	**0.57**	0.36-0.90
HDL cholesterol (≥50/60 mg/dL)	0.94	0.60-1.48	1.03	0.57-1.87	0.83	0.44-1.57
Current smoking	*0.73*	0.50-1.06	0.79	0.48-1.29	0.65	0.35-1.21
Physical activity (I-IV)	0.90	0.76-1.06	0.96	0.78-1.18	*0.77*	0.58-1.03
Abdominal obesity (≥95/88 cm)	**2.63**	1.89-3.66	**2.40**	1.55-3.73	**2.97**	1.78-4.96
Hypertension (140/90 mm Hg)	*1.39*	0.96-1.99	0.91	0.48-1.72	**1.74**	1.09-2.76
Apo A-I, mid tertile	1.21	0.84-1.74	0.85	0.50-1.44	*1.72*	1.01-2.94
Apo A-I, top tertile	**1.58**	1.10-2.27	1.35	0.83-2.20	**1.90**	1.10-3.28
Model 3[c]	*Total, n = 223/1740*[b]		*Men, n = 115/855*		*Women, n = 107/885*	
HDL cholesterol (35-50/40-60)	0.81	0.58-1.12	0.97	0.60-1.56	**0.71**	0.26-0.85
HDL cholesterol (≥50/60 mg/dL)	1.03	0.64-1.66	1.04	0.55-1.97	0.99	0.34-1.70
CRP[d]	**1.15**	1.05-1.17	*1.12*	0.97-1.26	**1.27**	1.06-1.50
Apo A-I, mid tertile	1.28	0.87-1.59	1.02	0.59-1.77	1.63	0.93-2.88
Apo A-I, top tertile	**1.80**	1.24-2.62	1.53	0.92-2.54	**2.14**	1.22-3.77

In mid/high HDL categories, 553/167 men and 699/176 women were encoded in model 1. In mid/high HDL categories, 65/110 men and 482/122 women were encoded and, in mid/top apo A-I tertiles, 329/313 men and 316/326 women were encoded in model 2. Referents: HDL cholesterol less than 35/40 mg/dL and apo A-I low tertile. Significant values are highlighted in bold.

[a] All models were adjusted also for sex (RR = 0.73, $P = .03$ in model 1), age, physical activity, and use of lipid-lowering drugs.

[b] Number of new diabetes/number at risk in model.

[c] Model 3 was adjusted also for abdominal obesity and hypertension.

[d] Log-transformed values, expressed in terms of a 3-fold increment.

with respect to cardiometabolic outcomes in the population at large, elicited by prospective epidemiology. The study further suggests that sex modulated the type of observed HDL dysfunctionality. The environment of highly prevalent MetS in this population sample presumably led to functional HDL alterations with ensuing impaired protection against cardiometabolic risk.

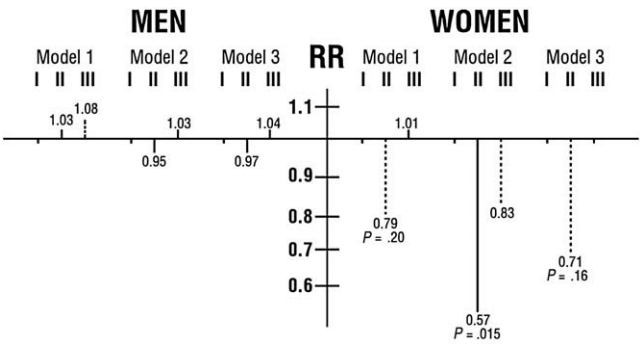

Fig. 1. Diagram depicts RRs of 3 HDL cholesterol categories for type 2 diabetes mellitus in men and women in 3 multivariable models. Referent is category I (<35/<40 mg/dL) with RR = 1.0. It is apparent that serum HDL cholesterol levels in men display no significant relationship to diabetes. By contrast, the intermediate category (II = 40/60 mg/dL) in women reveals a substantial decline in RR that becomes significant in model 2 when apo A-I tertiles are entered; yet protection is attenuated in the highest category (III = >60 mg/dL). See text for adjustments.

4.1. Sex-related HDL dysfunction assessed through cardiometabolic risk

Despite the fact that HDL's antioxidative deficiency has been extensively documented in atherogenic dyslipidemias using in vitro assays, direct evidence for its presence in vivo was lacking [22]. Hypertriglyceridemia, with concomitant modification of the HDL lipid core and conformational alteration of apo A-I, is currently identified as a driving force in the dysfunction of HDL particles in type 2 diabetes mellitus [7]. In evaluating the significance of HDL cholesterol levels, particle size, and apo A-I in 2 prospective studies [11], very high serum levels of HDL cholesterol were found to be positively associated with cardiovascular risk in the secondary prevention IDEAL study. Our findings suggest that increased cardiometabolic risk at high HDL cholesterol levels may occur in the general adult population in the absence of diabetes or CHD, perhaps in an environment of hypertriglyceridemia/elevated apo B and proinflammatory state. Evidences pointing to attenuated antiatherogenic and antioxidative/anti-inflammatory HDL functions were deduced by comparing sex-based findings.

Overall, serum HDL cholesterol appeared to be significantly atheroprotective in men, conferring 1.8% protection against incident CHD for a 1-mg/dL increment, when adjusted for traditional cardiovascular risk factors. High-density lipoprotein cholesterol did not prove to be protective against the development of CHD in Turkish women.

Conversely, in the sexes, whereas hardly any protection against diabetes was observed in the multivariable analysis among men in whom abdominal obesity was of overwhelming importance, substantial protection was detected in women having intermediate HDL cholesterol levels. The association reached significance when apo A-I tertiles were included, indicating that the diabetes-enhancing effect of elevated apo A-I levels was counteracted in women by HDL particles comprised in the intermediate category, though insufficiently by those in the highest category. Apolipoprotein A-I, not the topic in focus here, has newly been reported to be combined during oxidation to LDL (apo A-I–LDL), which could mark in a cross-sectional study coronary artery disease more accurately than CRP [23]. One may infer that, in men, antioxidative and anti-inflammatory HDL properties were primarily involved because no protection against diabetes was observed. Together with a diminished protection in women at levels greater than 60 mg/dL, these findings suggest that high HDL cholesterol values among Turks of both sexes may be heterogeneous with respect to several protective functions of HDL particles.

It is unclear why, in women, circulating HDL having dysfunctionality against diabetes is in essence also quantitatively increased; but that this may result from a slowness of its catabolism during the oxidative process may be conjectured, presumably similar to apo A-I. From our findings may also be deduced that HDL dysfunction as a risk factor for diabetes is much more prevalent in men than women.

A novel cell free assay and HDL inflammatory index were recently described to determine proinflammatory HDL. Dysfunctional HDL was found in half of participants with HDL inflammatory index of at least 1. Positive carotid intima-media thickness was associated with dysfunctional HDL after certain adjustments [24].

4.2. HDL's associations with inflammatory markers and other protective serum proteins

Aside from the epidemiologic evidence of the relative protection against cardiometabolic risk conferred by serum HDL cholesterol, the positive correlation observed between HDL cholesterol and fibrinogen, an inflammatory marker and acute phase reactant, and apo A-I, which is recognized by us as a factor enhancing cardiometabolic risk, and the weak inverse correlations with CRP may be cited as biological evidence of functional defectiveness of HDL in this cohort. In addition, HDL cholesterol was weakly correlated in women with obesity measures and less so with fasting insulin concentrations.

The herein reported evidence of lacking protection against cardiometabolic risk by HDL is not an isolated phenomenon in this population sample. High compared with low serum apo A-I levels nearly double the risk independently for incident diabetes, particularly in women, as also suggested in the current study. Furthermore, serum apo A-II concentrations, by conferring risk against MetS and diabetes, exhibit evidence of anti-inflammatory dysfunction; and the presumably dysfunctional HDL–apo C-III is a stronger predictor of type 2 diabetes mellitus than waist girth among Turks (as yet unpublished). Finally, Turkish women revealed potential anti-inflammatory dysfunction of serum adiponectin concentrations [25], which in men conferred little protection against diabetes and hypertension [14]. Collectively, these alterations suggest that, presumably in an environment of high prevalence of obesity and hypertriglyceridemic dyslipidemias, several defense mechanisms such as activities of circulating protective proteins may be seriously attenuated. The rapid increase of the prevalence of MetS in the 1990s [16], concomitant with increasing abdominal obesity and hypertriglyceridemia, is considered to have constituted a suitable environment.

Clinical implications of recognizing the possibility of impaired HDL cardioprotection are evident. Caution against undue reliance of high serum concentrations might be in place in ethnic groups in which this possibility has been demonstrated; other risk factors such as levels of accompanying apo A-I or triglycerides might then be taken into account in greater weight for cardiometabolic risk assessment. These findings emphasize the need for further research to improve the function of HDL particles using cholesteryl ester transfer protein inhibitors, niacin, recombinant HDL, or apo-mimetic peptides [23]. The hormonal mechanism possibly underlying the sex difference in these inflammation-modulated HDL activities also needs further investigation.

Lack of biological assays obviously deters us to assess functionality of HDL particles directly. The use of only 1 baseline value of serum HDL cholesterol, overlooking intraindividual variations, may be considered a further limitation, although it generally leads to a regression dilution effect rather than a systematic bias. The number of outcomes in the highest HDL cholesterol category in the sexes may be considered relatively small. However, adoption of lower cutoffs with essentially similar findings and multiplicity of sex-based asymmetrical findings with consistent direction, together with those reported previously, preclude them to be qualified as chance findings due to limited statistical power. The present findings may not fully apply to populations with a low prevalence of cardiometabolic disorders, but warrant, nonetheless, further investigation in this area. The strengths of the study include its prospective design and being based on a representative sample of a general population, incorporating also women, in which cardiometabolic disorders prevailed highly, and the adjustment for diverse relevant determinants of CHD and diabetes, all applied in a single cohort.

4.3. Conclusion

Protection by HDL particles against risk of type 2 diabetes mellitus and CHD is reduced in Turkish middle-aged and elderly adults, but not symmetrically in the sexes. Associations of HDL cholesterol with inflammatory markers and other protective proteins were consistent with an impaired HDL functionality that ultimately might result from an excess of chronic low-grade inflammation prevailing in this population sample.

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