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ScienceDirect
Metabolism Clinical and Experimental 60 (2011) 499–512
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Low-grade inflammation, and dysfunction of high-density lipoprotein and its apolipoproteins as a major driver of cardiometabolic risk

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Received 18 February 2010; accepted 19 April 2010

Abstract

Dysfunction of high-density lipoprotein (HDL) particles that even become proinflammatory or lose atheroprotective properties is known through analyses of HDL isolated from diabetic subjects. Recently, high concentrations of HDL or apolipoprotein (apo) A-I in individuals with diabetes or coronary heart disease were found to reveal dysfunction in some population-based studies. Such dysfunction of HDL and its apos A-I, A-II, and C-III has been observed in a general population for the first time among Turkish adults. Functional defectiveness manifested itself by unexpected correlations with inflammatory biomarkers and, in long-term follow-up, by lack of protection against diabetes and coronary heart disease, accounting for the excess incidences in Turks. Female sex was more pronouncedly affected by this process that presumably exists in other ethnicities in South Asia, East Europe, and the Middle East. In contradistinction, in Western and East Asian population, only individuals with glucose intolerance or those at risk for cardiometabolic disease are considered to be or were documented in a review of clinical trials to have been affected by impaired function of HDL. High-density lipoprotein dysfunctionality is closely linked to obesity and low-grade inflammation yet seems to act partly independently of them. Cigarette smoking in overweight women with low-grade inflammation appears to offer limited protection against cardiometabolic risk. The great impact in public health of the dysfunction of protective serum proteins requires individual clinical recognition, appropriate preventive measures, and delineation of management, including with anti-inflammatory drugs.

1. Introduction

The aim of this review is to summarize current knowledge on some novel mechanisms in the development of type 2 diabetes mellitus and coronary heart disease (CHD), with special reference to impaired function of high-density lipoprotein (HDL) and its apolipoproteins (apos) A-I, A-II, and C-III. Such dysfunction arises in a milieu of low-grade inflammation, itself known to enhance cardiometabolic disorders, namely, metabolic syndrome (MetS), diabetes, and CHD. The worldwide pandemic of obesity in the past decade or two has augmented the impact of cardiometabolic risk in public health and the associated concerns for health economics.

High-density lipoprotein particles are the mainstay of atheroprotective defense mechanisms in humans. Reverse cholesterol transport from the peripheral tissues is the best known and salient activity. Moreover, such diverse mechanisms as antioxidant and anti-inflammatory functions via paraoxonase [1] or apo A-I and A-II [2] have been demonstrated. High-density lipoproteins also inhibit cytokine-induced expression of endothelial cell adhesion proteins [3], reduce superoxide production [4], and neutralize C-reactive protein (CRP) proinflammatory activity [5]. High-density lipoproteins further possess inhibitory effects on thrombosis [6] and apoptosis [7].

However, under circumstances incompletely understood, atheroprotective activities of HDL may become deficient, a process designated as *HDL dysfunctionality*. Some of the novel information on HDL dysfunctionality was initially derived from patients with diabetes [8]. Cultures of HDL and apo A-I in arterial wall model or cell-free assays [9] as well as experiments in transgenic mice [10] have shed light on the

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0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2010.04.018

lack of anti-inflammatory and other properties of these proteins protecting against cardiometabolic risk. Torcetrapib, an inhibitor of cholesterol ester transfer protein, failed to induce regression of atherosclerosis via raising HDL levels [11], though possibly because of off-target toxicity of the molecule. Recently, HDL cholesterol (HDL-C) at high serum concentrations was documented by prospective epidemiology to be dysfunctional in CHD patients [12]. Further epidemiologic evidence for impaired protection against cardiometabolic risk by high HDL-C levels and certain apolipoproteins was provided firstly in a general population in the Turkish Adult Risk Factor (TARF) study. These observations on dysfunction of protective serum proteins drew attention to a predominant but not exclusive female sex specificity [13-15].

Additional to the impaired protection against cardiometabolic risk, correlation analyses of HDL-C/apo A-I with inflammatory biomarkers (such as fibrinogen or CRP) and with obesity measures or fasting insulin concentrations served as biological evidence of functional defectiveness of HDL among some Turkish adults. Finally, evidence was obtained suggesting that an environment that induced functional impairment of HDL and its constituents via low-grade inflammation and mechanisms further to be elucidated likely disclosed also a dysfunction of serum adiponectin [16] and a less hazardous or even beneficial effects of cigarette smoking on cardiometabolic risk.

1.1. The TARF study and characteristics of Turkish adults

The TARF study is a longitudinal population-based cohort study on the prevalence of cardiac disease and risk factors in adults in Turkey carried out biennially since 1990 in 59 communities scattered throughout all geographic regions of the country [17]. It involves a random sample of the Turkish adult population, representatively stratified for sex, age, and geographic regions and for rural-urban distribution [17]. Because waist circumference and serum HDL-C measurements were first performed at the follow-up visit in 1997/1998, the latter examination formed the baseline for the studies reported in this review. Participants, 28 years or older at baseline, were examined over a period of 11 years, up to the 2008/2009 survey. Data were obtained by history of the previous years via a questionnaire, physical examination of the cardiovascular system, sampling of blood, and recording of a resting 12-lead electrocardiogram [18].

We had pointed out in the TARF study that MetS [19] and type 2 diabetes mellitus were highly prevalent among Turkish adults. Among adults 30 years or older, the prevalence of MetS defined with Adult Treatment Panel III criteria was found to be 33% [19]; the prevalence rose 5 years later to 42% using the modified criteria of fasting glucose of at least 100 mg/dL (5.55 mmol/L) for prediabetes and, in men, waist circumference of at least 95 cm. The incidence of type 2 diabetes mellitus among adults aged 47 ± 11 years was 12.0 per 1000 persons per year, an incidence which is nearly 3-fold of that, say, in the United Kingdom.

Turks are recognized to have (by roughly 20%) lower levels of HDL-C than Westerners [20] and to possess among the highest CHD mortality in Europe [21]. The latter has not been shown to be attributable to decreasing concentrations of HDL-C or apo A-I. Low HDL-C levels are considered to be both genetically determined and secondary to the high prevalence of MetS.

2. Low-grade inflammation in impaired glucose metabolism

2.1. Low-grade inflammation in the development of glucose intolerance and type 2 diabetes mellitus

Elevated levels of circulating inflammatory cytokines such as tumor necrosis–α, interleukin (IL)-1, IL-6, or CRP, reflecting low-grade inflammation and associated with obesity, may promote insulin resistance in various tissues [22]. C-reactive protein can induce endothelial dysfunction by down-regulating the expression of endothelial nitric oxide synthase [23] or promoting the production of endothelial adhesion molecules to enhance insulin resistance [24]. Interleukin-6, involved in hepatic CRP synthesis, is also an adipocyte signaling molecule released from visceral and subcutaneous fat stores and is considered to modify glucose and lipid metabolism in adipocytes [25]. Elevated levels of IL-6 and CRP have been shown to predict independently diabetes risk in American postmenopausal women in a large case-control study [26]. In addition to the inflammatory cytokines, visceral obesity and atherogenic dyslipidemia associated with MetS modulate function and survival of the pancreatic β-cells. Whereas some free fatty acids (saturated palmitate) and lipoproteins are proapoptotic, others (oleate) are protective [27]. In the nondiabetic National Health and Nutrition Examination Survey III population sample, elevated CRP concentrations were associated with fasting glucose levels only in women [28], suggesting that the role of inflammation in glucose intolerance may be sex specific.

The important issue of the extent to which the association of low-grade inflammation with impaired glucose metabolism is independent of these and other conventional risk factors is still not settled.

Several population-based studies suggest an independent role for CRP in the development of insulin resistance and diabetes [29], but it is unclear whether this role is causal in the inflammatory cascade. A Mendelian randomization study using CRP gene haplotypes pointed to this association being likely noncausal and playing a causal role via upstream effectors [30]. Using 3 tagging single nucleotide polymorphisms in *CRP,* haplotypes were constructed and used in a pooled analysis of 5274 men and women in the Whitehall II and Northwick Park II studies for the association between CRP and diabetes, which produced null findings [30].

A prospective study and a derivation of an algorithm in the TARF indicated that CRP levels among Turks predict diabetes independently of potential confounders. A total of 1270 men and 1320 women were evaluated at a mean 4.3 years of follow-up [31]. A 3-fold increment in CRP levels adjusted for age, waist circumference, and fasting glucose predicted the development of diabetes with a hazard rate (HR) of 1.40 (95% confidence interval [CI], 1.16-1.69) in women but not in men. In a subsample in which baseline homeostasis model assessment (HOMA) values were available, prediction of diabetes by serum CRP was independent of HOMA [31].

Furthermore, the risk of diabetes mellitus was estimated in 2261 middle-aged TARF participants who were free of diabetes at baseline and were followed up over 7.6 years. Diabetes newly developed in 212 subjects. Cox proportional hazard regression and 15 variables were used to predict diabetes (unpublished observation; Onat A, Can G, Yüksel H, Ayhan E, Doğan Y, Hergenç G; "An algorithm to predict risk of type-2 diabetes in Turkish adults: contribution of C-reactive protein"). Height, family income brackets, systolic blood pressure, smoking status, alcohol use, and HDL-C levels, which have been significant predictors in other populations, were not independently predictive in either sex. Sex was a major predictor, along with family history of diabetes, fasting glucose, and waist circumference in both sexes, whereas non–HDL-C levels in men and physical inactivity and serum CRP were so in women only. C-reactive protein levels independently predicted diabetes with an HR of 1.43 (1.16-1.76) in women but not significantly in men (HR, 1.13 [0.95-1.34]). Area of the receiver operating characteristic curve of the final model was 0.783 in men and 0.772 in women ($P < .001$ each). An algorithm using the stated 7 variables (sex, family history of diabetes, fasting glucose, waist circumference, non–HDL-C, physical inactivity, and serum CRP) was developed separately for each sex (Table 1). Although several algorithms for the prediction of diabetes have been in use among Western populations, none has found serum CRP concentrations to be independently relevant as to incorporate into the algorithms.

Table 1
Algorithm for diabetes risk prediction among Turkish men and women (TARF data)

		Male	Female
Family history of diabetes	Yes	3	2
Physical activity	Yes	−1	−2
Age, y	41-50	1	0
	51-59	3	1
	≥60	2	0
Waist circumference, cm	93-103/88-101	1	3
	≥104/102	3	5
Fasting glucose, mmol/L	>5.55	3	2
CRP, mg/L	Male >0.8	2	
	Female 0.81-6.3		3
	≥6.3		5
Non–HDL-C, mmol/L	3.63-4.32	2	0
	≥4.32	2	1

Reference categories receive no points. A 15- to 42-fold spread in crude risk was observed across the quintiles of risk score in men and women.

2.2. CRP levels in Turks

In the adult population sample, geometric mean CRP levels were 1.77 ± 2.7 mg/L and 2.03 ± 2.9 mg/L, respectively, among more than 2600 Turkish men and women [31]. Values in men are 10% to 15% higher than those given for American or European men; those in women are approximately 25% higher than those for their female counterparts [32]. Although a sex difference hardly was provided for Westerners [32], a large meta-analysis recorded nearly 50% higher circulating CRP in women than men in Western populations [33].

2.3. Low-grade inflammation or oxidative stress in regard to CHD risk in hyperglycemic subjects

The independence of the role of low-grade inflammation/oxidation is particularly relevant in regard to the increased cardiovascular risk seen in diabetic individuals that is far from being fully explained by traditional risk factors. Oxidized lipoproteins induce adherence between endothelial cells and monocytes, recruit monocyte-derived macrophages into the arterial wall, and form foam cells of macrophages. Oxidative stress may contribute to atherogenesis by mechanisms other than low-density lipoprotein (LDL) oxidation. Free radical oxygen species such as superoxide anion can react with and inactivate nitric oxide, promoting proatherogenic mechanisms, mainly endothelial dysfunction [34]. Furthermore, data are emerging that atherogenic dyslipidemia can reduce endogenous anti-inflammatory pathways mediated by HDL and amplify proinflammatory actions of very low-density lipoprotein [35]. Very low-density lipoprotein that bears apo C-III can induce expression of vascular cell adhesion molecule–1 in vascular endothelial cells and increase adhesion of monocytic cells via stimulating nuclear factor–κB [36,37].

This issue of endothelial dysfunction and low-grade inflammation has been investigated in a nearly 12-year follow-up of 631 elderly white men and women of the Hoorn Study [38]. They used z scores (mean SD scores) for CRP and soluble intercellular adhesion molecule–1 as markers of low-grade inflammation. In cross-sectional analysis, subjects with both prediabetes and diabetes were significantly and independently associated with low-grade inflammation. In addition, diabetes was associated with markers of endothelial dysfunction (von Willebrand factor and soluble vascular cell adhesion molecule–1). In their longitudinal analysis, they provided findings that were interpreted as endothelial dysfunction and low-grade inflammation explaining approximately 43% of the increase in cardiovascular mortality conferred by diabetes. Prediabetes was not clearly associated with an increased mortality risk, but the power of this aspect of the study was limited.

Studies have shown that 2-hour glucose is a stronger risk predictor than fasting glucose for both incident CHD and cardiovascular disease (CVD) mortality [39]. Based on 7 to 10 years of follow-up of 5 Finnish cohorts, it was demonstrated that the HR for 1-SD increment in 2-hour postload glucose was 1.17 (95% CI, 1.05-1.30) for CHD incidence and slightly higher for cardiovascular mortality, whereas for fasting glucose, HRs were 1.05 (0.94-1.17) and 1.13 (1.01-1.25). Similar results were obtained in Japanese [40] and Dutch [38] studies. Results were independent of traditional risk factors, but the role of inflammation had not been studied. An atherogenic risk factor profile was observed in a cross-sectional study in the 266 offspring of diabetic patients who had normal glucose tolerance and whose 2-hour postload glucose did not return to the fasting level [41].

2.4. Degree of independence of low-grade inflammation for cardiovascular and metabolic risk from obesity and insulin resistance in the general population

With respect to the prediction of CHD, CRP has been determined in a comprehensive new meta-analysis to be an independent predictor [33]. After adjustment for age, sex, and CHD risk factors including body mass index (BMI), an HR of 1.41 (1.30-1.53) corresponded to a 3-fold increment in CRP.

Out of an analysis of 14 cardiovascular risk variables among Turks, 7 were warranted as independent factors to be included in a CHD prediction model. Previous analyses had demonstrated that waist circumference was not an independent CHD predictor in women in models that included diabetes and/or CRP levels. Table 2 shows that HDL-C and smoking were not significant in women in whom elevated CRP revealed a more than 2-fold CHD risk compared with a level of less than 0.8 mg/L in Cox proportional-hazard models. The significant CHD risk of circulating CRP stood in contrast to the nonsignificant LDL cholesterol (LDL-C) concentrations.

2.5. Independence from obesity of low-grade inflammation for cardiometabolic risk in impaired glucose tolerance

In the Diabetes Epidemiology: Collaborative analysis of diagnostic criteria in Europe (DECODE) study, the impaired glucose tolerance (IGT) category clearly distinguished itself by lacking a relationship between dyslipidemia and CHD incidence from the other glucose categories (personal communication, 2010; Zhang L, Qiao Q, Laatikainen T, et al; "The impact of dyslipidaemia on incidence of coronary heart disease in Finns and Swedes with different categories of glucose tolerance"), suggesting that other mechanisms, those related to a proinflammatory status/oxidative stress, were more important. The virtual absence of an inverse relation between HDL-C and CHD incidence supported the notion that HDL particles were dysfunctional in this setting. As judged from CHD incidence, IGT was 45% more atherogenic than isolated impaired fasting glucose.

Subjects with IGT may have higher remnant lipoproteins and oxidative stress than individuals with a normal

Table 2
Cox regression analysis of HDL-C and other risk factors at baseline for incident CHD (TARF data)

	β	HR	95% CI	β	HR	95% CI
	Men, n = 158/1043[a]			Women, n = 144/1189		
Age, y						
40-49	1.36	**3.89**	1.95-7.76	1.27	**3.55**	1.34-9.40
50-59	1.60	**4.95**	2.45-9.99	2.17	**8.74**	3.39-22.5
≥60	2.09	**8.09**	4.01-16.3	2.35	**10.5**	4.04-27.5
Presence of diabetes	0.794	**2.21**	1.25-3.92	0.925	**2.52**	1.58-4.03
LDL-C, mg/dL						
100-130	−0.261	0.77	0.49-1.21	0.27	1.31	0.79-2.17
≥130	0.725	**2.06**	1.38-3.09	0.358	1.43	0.87-2.35
SBP, mm Hg						
120-139	0.351	1.42	0.93-2.16	0.735	**2.09**	1.17-3.71
140-159	0.476	1.61	1.00-2.60	0.171	1.19	0.61-2.30
≥160	1.293	**3.64**	2.20-6.04	1.255	**3.51**	1.96-6.29
Ever vs never smokers	0.452	**1.57**	1.06-2.32	−0.183	0.83	0.50-1.38
HDL-C, mg/dL						
40-49/50-59	0.474	1.61	0.85-3.03	0.242	1.27	0.72-2.26
<40/<50	0.57	1.77	1.00-3.13	0.158	1.17	0.66-1.08
CRP[b], mg/L						
0.8-1.4/1.6	0.045	1.05	0.59-1.85	0.475	1.61	0.74-3.51
1.41-2.8/1.61-3.2	−0.105	0.90	0.52-1.55	0.231	1.26	0.58-2.74
2.8-4.99/3.21-6.3	0.674	**1.96**	1.16-3.31	0.756	2.03	0.97-4.25
>5/>6.3	0.485	1.62	0.98-2.68	0.953	**2.59**	1.25-5.38

Significant values are highlighted in bold. Reference categories were as follows: age 30 to 39 years, nondiabetic, LDL-C <100 mg/dL, SBP <120 mm Hg, nonsmoker, HDL-C ≥50/60 mg/dL, CRP <0.8 mg/L. SBP indicates systolic blood pressure.

[a] Incident CHD/number at risk.

[b] Log-transformed values.

response to glucose loading. The Copenhagen City Heart Study showed prospectively that high nonfasting triglyceride (Trg) levels predicted myocardial infarction, CHD and death [42], and ischemic stroke [43] independently of conventional risk factors. This effect was more pronounced in women and was attributed to the coexisting remnant lipoproteins. They did not examine the role of inflammatory biomarkers in this study.

We hypothesize that individuals with a tendency for IGT (having 2-h plasma glucose > fasting plasma glucose) also represent a condition associated with chronic low-grade inflammation independent of obesity and insulin resistance, which accounts for the elevated CVD mortality of this group (like the excess CVD events in diabetes not adequately accounted for by conventional risk factors). Women are more prone to low-grade inflammation [13,31,44] and to tendency for IGT. We have found serum complement C3 to be a significant predictor of future CHD independent of current smoking, CRP levels, and the identified MetS [44].

2.6. Low-grade inflammation in relation to MetS

Baseline CRP levels predicted atherogenic dyslipidemia, when adjusted for age, baseline dyslipidemia values, and apo B tertiles, independent of age, waist circumference, and smoking status. After adjustment for sex, age, and the 5 MetS components, CRP among 1090 Turkish men and women free of MetS at baseline predicted newly developing MetS, with an HR of 1.16 (95% CI, 1.02-1.32) [31]. This was the first study documenting that CRP predicted future MetS independent of age and its 5 components, suggested that CRP was an additional MetS component in Turks. Previous prospective studies had not fully adjusted for the MetS components: in the Mexican population sample, in which MetS was defined in the absence of abdominal obesity, CRP was found to be a predictor in women but not in men [45]. The risk of MetS was several-fold higher with elevated CRP concentrations in a Finnish study that was confined to men [46].

Examining the association between circulating CRP and MetS phenotypes and findings from a Mendelian randomization approach in the British Women's Heart and Health Study suggested that the association was likely noncausal [47]. The applicability of this conclusion to different ethnicities remains to be determined, although other biomarkers of subclinical inflammation mediating CHD should also be investigated.

2.7. Sex difference in the independence of inflammation from insulin resistance and in its role in the development of diabetes

The reason why serum CRP as an inflammatory biomarker was an independent MetS component in each sex among Turks, whereas it predicted diabetes independently only in women, may be the following. First, proinflammatory status and insulin resistance are likely to be tightly linked to each other in men, together driving diabetes. In contrast, proinflammatory status acts largely independently of insulin resistance in women, in whom diabetes develops in a process wherein insulin resistance may be less prominent. This explanation largely accounts also for the sex difference in the development of diabetes from obesity and MetS [48]: whereas women go on from obesity directly into diabetes, men primarily with MetS develop diabetes.

A second reason may be the higher magnitude of CRP levels in diabetic women than in diabetic men. The independent influence of inflammatory mediators on diabetes in women (Fig. 1) may reflect the activity of endothelial macrophages and adhesion molecules. Very low-density lipoprotein and LDL isolated from sera of patients with diabetes or MetS are more susceptible to lipolysis by circulating and subendothelial secretory phospholipase A_2 group V [49], leading to elevations in nonesterified fatty acids and lysophosphatidylcholine in the lipoproteins and contributing to a proinflammatory state [50]. This susceptibility may have greater relevance in women.

A similar sex difference has been reported in the cross-sectional Health, Aging, and Body Composition study [51] on 2683 elderly white and black Americans: diabetes likelihood was associated with high CRP (>3.1 mg/L) in women, but not in men, independently of total body fat and computed tomography–assessed visceral fat among other confounders.

2.8. Relation of sex, smoking status, and sex hormone–binding globulin levels to low-grade inflammation and cardiometabolic risk

Interestingly, smoking Turkish men had higher age-adjusted CRP concentrations (1.96 ± 1.04 mg/L, $P < .001$), whereas smoking women (n = 237) had lower CRP (1.75 ± 1.07 mg/L, $P = .027$), than never-smoked counterparts [31]. A tendency to

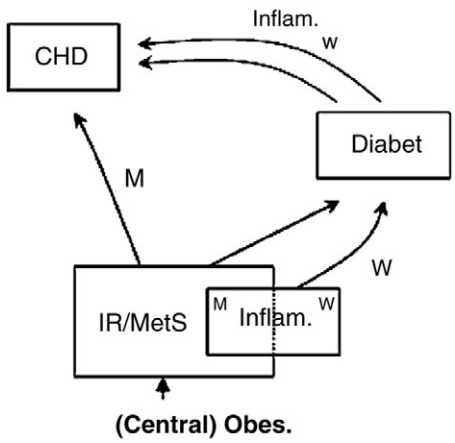

Fig. 1. The sex difference concerning low-grade inflammation, a component of the insulin resistance/MetS among Turks. Low-grade inflammation in women has an important additional independent component that enhances the development of type 2 diabetes mellitus and, in turn, CHD.

a similar constellation has also been recorded in a large meta-analysis on circulating CRP in more than 160 000 participants [33] in which, compared with nonsmokers, male current smokers had roughly 19% higher (~1.46 vs 1.73 mg/L), whereas female current smokers had similar or marginally lower (~2.17 vs 2.13 mg/L), CRP levels.

This lack of unfavorable relationship of smoking with CRP in Turkish women may partly account for their partial protection against the development of diabetes [52]. In the prediction of MetS, heavy smoking was significantly "protective" (relative risk [RR], 0.50 [95% CI, 0.26-0.94]) in women and in both sexes combined after adjustment for age, baseline family income bracket, and physical activity grade [52]. As predictor of new diabetes, heavy smoking was significantly "protective" (RR, 0.54 [95% CI, 0.35-0.83]) in all adults after similar adjustment. Additional adjustment for insulin and CRP levels hardly modified the RRs in women. Age-adjusted RR of smoking less than 25 cigarettes daily for incident diabetes was significantly reduced compared with never smokers also among more than 114 000 US women during 12 years of follow-up [53].

The beneficial effect is in part via protection against obesity. We have documented a modest independent favorable effect of smoking in women on serum complement C3 [44] and on accumulation of visceral fat [54] and, in both sexes, against development of hypertension [55] and on lowering of serum concentrations of apo C-III [56] (which appears to be related additionally to the T homozygosity of the *APOC3*-482C>T polymorphism). This ethnicity-based difference contrasts with the report on more than 2300 British men wherein carriers of a -482T allele responded to smoking with a 20% increase in serum Trg [57]. Nicotine was shown to reduce inflammation in inflammatory bowel disease of rats [58] and to suppress in human endothelial culture the production of proinflammatory cytokines via nicotinic acetylcholine receptor expressed by macrophages during inflammation [59]. Moreover, mice developed collagen-induced arthritis at a delayed onset in those exposed to cigarette smoke or nicotine compared with nonsmoking controls [60].

The odds of low sex hormone–binding globulin (SHBG) concentrations (<45 nmol/L in men, <55 nmol/L in women) for the likelihood of 2 types of dyslipidemias, MetS and diabetes, were examined by regression analyses in models including age, smoking status, presence of abdominal obesity, and HOMA of insulin resistance [61]. In both sexes, low SHBG was associated independently with high-Trg, low-HDL dyslipidemia and with MetS, at significant odds ratios, independent of waist circumference or HOMA of insulin resistance. Low SHBG among women was additionally associated with the likelihood of diabetes when adjusted for the same confounders. It was concluded that low SHBG may be an important independent factor for cardiometabolic risk, particularly in women.

In a recent nested case-control study of US adults by Ding and associates [62], serum SHBG levels in postmenopausal women in the lowest quartile (<27 nmol/L) and in men in the bottom half (<26 nmol/L) indicated substantially increased risk for diabetes. The additive relevance to the risk of diabetes is less in men, similar to our analysis among Turks, than in women, in whom SHBG concentrations may be more related to small, dense LDL particles. The direct application of this finding may be most useful in nonobese women, regardless of accompanying markers of insulin resistance, a condition in which low SHBG levels may indicate clearly a higher diabetes risk.

3. Dysfunction of HDL and apolipoproteins

3.1. In vitro and animal experimental evidence of dysfunction of HDL and apo A-I

Using an in vitro reconstituted artery wall model by coculturing smooth muscle cells and endothelial cells or by other methods, Navab and coworkers [63] assayed the anti-inflammatory activity of HDL. High-density lipoprotein was shown to lose its anti-inflammatory properties in a milieu of inflammation [63] or in apo A-II transgenic mice [10].

3.2. Dysfunction of HDL and apo A-I in humans

In patients with diabetes, glycation of HDL-associated enzymes and especially of apo A-I depended on glucose concentration and was augmented in the presence of phospholipids [8]. Deficient anti-inflammatory properties of HDL in type 2 diabetes mellitus have been 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 [64]. The topics of oxidized phospholipids and HDL [65] as well as dysfunctional HDL as a diagnostic and therapeutic target have been reviewed [66]. Recently, HDL in high concentrations in patients with coronary artery disease (CAD) were also shown in coculture assays to possess less anti-inflammatory activity than in healthy controls, thus documenting that HDL was dysfunctional [9].

An evaluation of 3 major cardiovascular risk equations in patients with type 2 diabetes mellitus using UK Prospective Diabetes Study data reached the conclusion that the Framingham, Systematic Coronary Risk Evaluation (SCORE), and DECODE risk equations did not provide reliable estimates in diabetic individuals of either sex with respect to 10-year fatal cardiovascular or fatal CHD event rate [67]. Although the authors did not investigate, or comment on, the potential roles of HDL dysfunction, this is likely the main underlying reason.

3.3. Epidemiologic evidence of lack of protection against cardiometabolic risk by HDL and its apoproteins

It is held that each 1-mg/dL (0.026-mmol/L) increase in HDL-C level is associated with a 2% to 3% decrease in the multiadjusted risk of CHD. Consequently, it was stated in the

National Cholesterol Education Program Adult Treatment Panel III that HDL-C concentrations in excess of 60 mg/dL (1.55 mmol/L) counteract 1 risk factor [68].

The universality of this knowledge was challenged recently in some epidemiologic studies. In evaluating the significance for cardiovascular risk of HDL-C levels, particle size, and apo A-I in 2 prospective studies (Incremental Decrease in Endpoints through Aggressive Lipid Lowering [IDEAL] and European Prospective Investigation into Cancer and Nutrition [EPIC]-Norfolk), very high serum HDL-C levels (>70 mg/dL= 1.8 mmol/L) as well as the highest categories of HDL particle size were found to be positively associated with cardiovascular risk [12]. High HDL-C did not protect against CAD when associated with combined cholesterol ester transfer protein and hepatic lipase gene variants in the Regression Growth Evaluation Statin Study (REGRESS) study [11]. A recent systematic review and meta-analysis examined in 108 randomized trials involving 299 310 participants the extent to which changes in HDL-C altered CHD events [69]. It disclosed that no association existed between treatment-induced change in HDL-C and risk ratios for CVD morbidity and mortality when changes in LDL-C were adjusted for.

A series of outcome studies in the TARF study also disclosed that the above-stated basic knowledge is not necessarily so only in patients with CHD or diabetes or in individuals at risk for these disorders but even in the population at large [13,14]. Table 3 indicates that HDL-C concentrations significantly protected men against CHD (for a 12-mg/dL [0.3-mmol/L] increment; RR, 0.80 [95% CI, 0.69-0.95]) in 2 models independently of circulating CRP. In women, HDL-C levels were not associated with incident CHD.

In the prediction of diabetes, 2 models were used for apo A-I tertiles (Table 4): a basic one adjusted for sex, age, BMI, and use of lipid-lowering drugs (model 1) and one additionally adjusted for smoking status, CRP, and HDL-C levels (model 2) [14]. In both models, the top apo A-I tertile was significantly and independently associated with future risk of diabetes in men and women combined, at an RR of 1.7 to 1.9; and the mid tertile exhibited an insignificantly elevated RR. In men and women separately, similarly elevated significant RRs were observed.

It may be pointed out as a partial explanation to our observations that apo A-I has recently been reported to be combined during oxidation to LDL (apo A-I–LDL), high levels of which could mark in a cross-sectional study CAD more accurately than CRP [70].

Table 4
Multiadjusted prediction of incident type 2 diabetes mellitus by apo A-I tertiles at baseline [14]

	Total		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI
Model 1, n = 952 M + 964 F						
Apo A-I mid tertile	1.32	0.89-1.95	1.19	0.68-2.08	1.45	0.84-2.49
Apo A-I top tertile	1.66	1.15-2.42	1.78	1.05-3.00	1.54	0.90-2.63
BMI, kg/m^2	1.11	1.08-1.14	1.13	1.08-1.20	1.10	1.06-1.14
Model 2, n = 828 M + 851 F						
Apo A-I mid tertile	1.40	0.92-2.14	1.33	0.72-2.44	1.50	0.82-2.73
Apo A-I top tertile	1.98	1.31-3.00	1.90	1.06-3.42	2.02	1.12-3.65
BMI, kg/m^2	1.10	1.06-1.14	1.13	1.07-1.20	1.08	1.04-1.13
CRP[a] 2-fold	1.06	0.99-1.14	1.04	0.95-1.14	1.09	0.99-1.21
HDL-C, mg/dL	1.00	0.99-1.02	1.01	0.99-1.04	0.99	0.97-1.01

Model 1 included 108 men and 108 women with incident diabetes. Models included adjustments for sex, age, and (the significantly positively associated) lipid-lowering drugs (used by 56 men and 84 women in model 1).
[a] Log-transformed.

Table 3
Logistic regression analysis of HDL-C and other risk factors for incident CHD, at baseline [13]

	RR	95% CI	RR	95% CI	RR	95% CI
Model 1	Total, n = 408/3035[a]		Men, n = 221/1492		Women, n = 187/1543	
HDL-C, 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	Total, n = 365/2595[a]		Men, n = 198/1267		Women, n = 167/1328	
HDL-C, 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	NS
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[b]	**1.15**	1.08-1.23	**1.14**	1.03-1.25	**1.19**	1.08-1.33

Significant values are highlighted in bold. Encoded in model 1 were 805 and 289 current smokers, and 60 and 87 with diabetes mellitus.
*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.
[a] Number of new CHD/number at risk in model.
[b] Log-transformed values and expressed in terms of a 1-SD (3-fold) increment.

Table 5
Correlation of serum HDL-C with certain risk variables [13]

	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
BMI, kg/m^2	3035	−0.21	<.001	−0.12	<.001
Fasting Trg, 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,[b] mg/dL	1985	−0.11	.002	−0.08	.013
Fibrinogen, g/L	2148	0.06	.062	0.11	<.001
LDL-C, mg/dL	2645	−0.04	0.17	−0.06	.034
CRP,[a] mg/L	2595	−0.05	.08	−0.05	.048
Fasting glucose,[b] mg/dL	2595	−0.02	.54	−0.00	.90

[a] Log-transformed.
[b] Unspecified numbers are 3035.

3.4. Apo C-III in HDL acting as a diabetogenic factor

Apolipoprotein C-III in HDL is considered to have atheroprotective properties [71]. However, at a follow-up of 4.4 years of 802 Turks in whom apo C-III was measured by turbidimetric immunoassay, high apo C-III levels emerged as a major diabetogenic factor [56]. High tertile of apo C-III in HDL independently predicted newly developed diabetes, with a 2.5-fold RR for 1-SD increment (95% CI, 1.5-4.0) in combined sexes after adjustment for waist circumference, HDL-C, and other confounders. It constituted a better predictor than waist girth. Interestingly, both fractions of apo C-III were significantly and linearly associated with circulating complement C3 and alcohol use and inversely associated with smoking status. It was demonstrated that apo C-III is increased in serum from type 1 diabetes mellitus adults and that this serum factor promoted Ca^{2+}-dependent β-cell death in cultured mouse pancreas [72]. We believe that dysfunctionality of apo C-III in HDL carries huge public health implications among Turks.

3.5. Correlations of HDL-C and apolipoproteins with inflammatory biomarkers

Serum HDL-C was positively correlated with fibrinogen, an inflammatory marker and acute phase reactant, and was inversely albeit only weakly correlated with CRP [13], observations that may be cited as biological evidence of functional defectiveness of HDL (Table 5). In addition, HDL was weakly correlated in women with obesity measures compared with men and was not correlated with fasting insulin concentrations.

In a multiple linear regression analysis, apo A-I levels were positively correlated with female sex and systolic blood pressure and, in women, tended to a positive association with CRP (Table 6), suggesting assumption of proinflammatory properties [14]. Newly developed hypertension is partly determined in Turkish women by CRP independently of waist circumference and HOMA index [55], supporting a proinflammatory endothelial activation by serum apo A-I.

3.6. HDL dysfunction due to specific haptoglobin genotype

Haptoglobin, which binds hemoglobin to apo A-I, contains heme iron, a powerful oxidant. Hemoglobin and lipid peroxidases in HDL were elevated and HDL function was found to be impaired in Israeli subjects with diabetes (like in experimental mice), indicating that the prooxidant hemoglobin converted HDL to a prooxidant structure [73]. Haptoglobin and apo A-I are considered to inhibit the activity of lecithin cholesterol acyltransferase (LCAT) and, in persons with hyperlipidemia, the activity of phospholipid transfer protein (PLTP), thus reducing reverse cholesterol transport [74]. High-density lipoprotein dysfunction, secondary to haptoglobin with a 2-2 genotype, could be improved by supplementing vitamin E [73].

3.7. Evidence of HDL dysfunction in other (general) populations

Several reports from the Tehran Lipid and Glucose study disclosed that male and female residents of Tehran have low levels of serum HDL-C [75], similarly to Turks. Importantly, it was noted in prospective analyses that HDL-C did not significantly predict newly developing CVD in diabetic men and women and in the nondiabetic female sample [75]. Yet CHD risk was nearly 2-fold higher in women than in men.

Diabetes has long been recognized to be a stronger predictor for CHD or CHD mortality in women than in men. The otherwise existing sex gap in CHD risk is strongly attenuated in

Table 6
Multiple linear regression analysis for serum apolipoprotein A-I (in milligrams per deciliter) at baseline [14]

Independent variables	Total, n =1840		Men, n = 898		Women, n = 942	
	β coefficient	*P* value	β coefficient	*P* value	β coefficient	*P* value
Sex, F	13.1	.000				
Age, y	0.15	.033	0.16	.077	0.13	.21
Physical activity grade, I-IV	−0.9	.28	−1.2	.21	−0.5	.73
Current smoking, 0-2	−2.15	.000	−1.86	.009	−2.8	.011
Alcohol intake category, 0-3	6.0	.000	6.0	.000	5.7	.19
Systolic BP, mm Hg	0.12	.001	0.05	.31	0.16	.001
CRP[a]	0.83	.79	−1.26	.12	1.29	.11

All 3 regression models were significant at <.001 level. Model in total cohort explained 8% of variance in apo A-I.
[a] Log-transformed values expressed in terms of a 2-fold increment.

the presence of diabetes [76,77]. Greater tendency in women for abnormalities in lipids and lipoproteins and more frequent endothelial dysfunction have been postulated [76,77], for which HDL dysfunction might have been the main element. This point deserves to be studied further among Western populations in subjects with dysglycemia.

Lack of protection against cardiometabolic disorders can be discerned in population studies only with respect to high but not quite to intermediary or low concentrations (the referent category) of HDL-C, although the dysfunctionality might appear a priori to be fairly evenly distributed among HDL particles. However, it has been demonstrated in experiments on human PLTP/apo A-I double-transgenic mice that PLTP (which binds directly to apo A-I) together with human apo A-I results in formation of large cholesterol-enriched atherogenic HDL particles [78]. This, if valid under certain circumstances in humans, may constitute the link to dysfunctional HDL being more likely found in the high–HDL-C category.

4. Hypothesis

We hypothesize that, in a substantial proportion of middle-aged and elderly Turkish population, a proinflammatory/prooxidative state prevails that is related to a high prevalence of obesity and MetS. Under these circumstances, HDL particles and their apos A-I, A-II, and C-III (and likely serum adiponectin) lose their anti-inflammatory and atheroprotective properties (Fig. 2). The balance between apo B–containing lipoproteins and reverse cholesterol transport, as well as that between anti-inflammatory and proinflammatory processes, is tilted toward the enhanced development of diabetes and/or CHD.

Underlying this situation is presumably an excess PLTP activity in plasma. Plasma PLTP activity has been found to

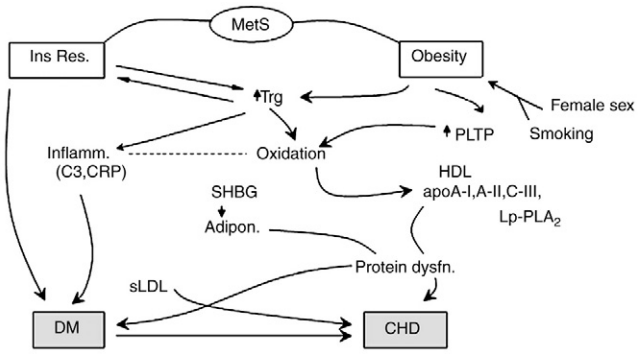

Fig. 2. The hypothesized interplay of pathogenic factors in enhanced cardiometabolic risk in a population with prevailing MetS. The central roles of low-grade inflammation/oxidation and dysfunctions of HDL, its apoproteins, and adiponectin are depicted. The presumed underlying influence of elevated circulating PLTP as well as of sex and SHBG is illustrated. DM indicates type 2 diabetes mellitus; Ins Res, insulin resistance; Lp-PLA_2, lipoprotein-associated phospholipase A_2; sLDL, small LDL particles.

be associated in linear models (among other inflammatory markers) best with CRP in patients with CVD and low HDL-C, independent of traditional risk factors and insulin resistance [79]. C-reactive protein proved to be an independent predictor of type 2 diabetes mellitus and CHD among Turks [31]. Phospholipid transfer protein activity was shown to be associated with several components of MetS [80]. A positive correlation of PLTP activity with Trg and an inverse one with HDL-C present in control subjects were lacking in patients with CAD, and the inverse correlation with apo A-I levels in controls was even positive in patients [81]. Cardiometabolic risk, especially type 2 diabetes mellitus, is predicted among Turks, in agreement with the stated observations, poorly by HDL-C but rather by high apo A-I levels [13,14]. Dysfunctions of serum HDL and its apolipoproteins are consistent with a prooxidant role of PLTP mediating reduced availability of vitamin E to apo B–containing lipoproteins [82].

A stronger influence of impaired anti-inflammatory processes and of oxidative stress relative to cardiometabolic risk in Turkish women than in men is in line with the finding that increase in CAD risk per quintile increment in PLTP activity was associated more strongly in women than in men [77]. Current cigarette smoking induces a greater reduction in adiposity and visceral adiposity in Turkish women than men; is associated with no rise in proinflammatory state; and given the more prominent proinflammatory state in women, exerts a more favorable influence on innate immunity, as assessed by a reduction of circulating complement C3 [44].

4.1. Ethnic differences in extent of inflammatory features of glucose intolerance

Dysfunction of HDL and apo A-I has been described and recognized in Westerners who have diabetes and/or CHD, as reviewed above. Epidemiologic evidence of HDL dysfunction seems to be distinguishing subjects with IGT from those with simple impaired fasting glucose. Abnormal HDL function has recently been shown to be associated with poor disease control and with significantly higher levels of haptoglobin and apo A-I in patients with rheumatoid arthritis, an active form of which disease increases cardiovascular morbidity and mortality [83].

Turkish adults are much more prone than Westerners to atherogenic dyslipidemia in the general population, leading to excessively high cardiometabolic risk. This may be partly accounted for by the more common minor allele frequencies of the -1131T>C and c.56C>G polymorphisms of the apo A-5 gene observed in them [84], which are known to be strong genetic determinants of serum Trg concentrations. Hypertriglyceridemia may remodel HDL particles, rendering them smaller and denser with concomitant impairment of function [64]. South Asian immigrants in the United States have also demonstrated evidence of proinflammatory HDL that was associated with increased carotid intima-media thickness [85]. Primary genetic insulin resistance and/or concurrent

systemic inflammation may have greater relevance in the development of diabetes among Indians [86]. The recently reported observation that the CVD rate in Eastern Europe for a given abdominal obesity was substantially higher than that in Northwest or Southern Europe [87] suggests that the proinflammatory state and, possibly, HDL dysfunction may be an added driver of risk among general adults. In contrast, such risks are observed in Westerners and East Asians thus far only in those with glucose intolerance.

5. Implications

Recognition of the important role of systemic inflammation and dysfunction of protective serum proteins as a major driver of cardiometabolic risk affects risk assessment and the public health, exhibiting an impact on the incidence of diabetes and CHD and on specific measures to be taken in the prevention and management of these diseases.

In the assessment of risks of diabetes and CHD, conventional algorithms are likely to have shortcomings in subsets of populations with HDL dysfunction and will require supplementation with an inflammatory biomarker, usually CRP, as was the case in Turkish adults. Algorithms for diabetes (Table 1) and CHD incorporate CRP for optimal prediction of the cardiometabolic risk.

Based on evaluation of hazard ratios, the impact of dysfunction of protective serum proteins on the incidence of diabetes and CHD is huge. Half of incident cases of diabetes and about one quarter of all new cases of CHD are estimated to be attributable to this impaired function of protective serum proteins among Turks.

5.1. Criteria for clinical suspicion of HDL dysfunction

The clinical implications of recognizing the possibility of impaired HDL cardioprotection are evident. Caution against undue reliance on high serum concentrations might be in place in ethnic groups in which this possibility has been demonstrated. Criteria for clinically suspecting dysfunction of protective serum proteins on an individual basis need be developed in such ethnic groups. We have found useful the following provisional criteria among Turks, which need to be further documented. In abdominally obese men older than 45 years, a Trg/HDL-C ratio of at least 6 is suspect. In obese women older than 50 years, a Trg/HDL-C ratio greater than 2.6, circulating CRP greater than 2.0 mg/L, Trg greater than 150 mg/dL (1.7 mmol/L), complement C3 greater than 1.3 g/L, or presence of MetS is also suspect of impaired function of the accompanying high HDL-C concentrations.

5.2. Prevention and management

An implication related to preventing cardiometabolic risk is that, in view of the susceptibility of the female sex to enhanced low-grade inflammation and serum protein dysfunction, best reflected by plasma atherogenic index (Trg/HDL-C ratio) [88], in ethnicities with a high prevalence of MetS, criteria of the upper normal limit of fasting serum Trg should be reduced to 1.4 mmol/L (124 mg/dL) in women, in contrast to retaining the present 1.7 mmol/L in men [67].

Intensive *lifestyle intervention* consisting of low-fat diet and moderate physical activity is mandatory. Such intervention reduced levels of both CRP and fibrinogen relative to placebo (and, to a lesser degree, to metformin) in a trial comprising more than 3200 women and men with IGT [89].

The documented presence of low-grade inflammation and dysfunction of protective serum proteins independent of obesity and insulin resistance stipulates that its management should incorporate agents targeting systemic inflammation.

Statins are known to increase levels of HDL-C and reduce Trg in MetS patients [90,91]; they are also recognized to reduce serum CRP (Table 7). This has been shown in the large Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of apparently healthy men and women without hyperlipidemia but with elevated CRP (≥2 mg/L) levels with rosuvastatin (20 mg daily) that not only halved the CRP levels but also reduced the primary end point of CVD and death, attaining an HR of 0.56 (0.46-0.69) [92]. However, further specific trials are needed in view of the new meta-analysis revealing a slightly increased risk of incident diabetes (odds ratio, 1.09 [95% CI, 1.02-1.17]) in more than 91,000 nondiabetic individuals who took part in randomized trials of statin therapy during a mean of 4 years [93]. Moreover, the influence of pravastatin and atorvastatin on markers of oxidative stress in hypercholesterolemic subjects has been variable, reducing oxidized LDL and lipoprotein-associated phospholipase A_2 but not affecting other markers; thus, their clinical utility is not yet defined [94].

Most commonly used antioxidants are supplements of vitamin E, vitamin C, and β-carotene. Clinical trials have not demonstrated consistent beneficial effects of antioxidants on cardiovascular outcomes [35], despite evidence of improvement in insulin action in healthy or diabetic subjects. Omega-3 fatty acids have an established importance for plaque stability [95], upon which probably rests its antiarrhythmic effects, and reduction of cardiac events in clinical trials. But the risk of coronary disease was not significantly associated in men with dietary intake of *n*-3 fatty acids or fish intake in the large Health Professionals' study [96], nor did intake of omega-3 fatty acids protect against atherosclerotic plaque formation in Alaskan Eskimos [97].

Table 7
Potential treatment options in individuals with HDL dysfunction

- Fish oil (omega-3 fatty acids)
- Statins or fibrates
- Niacin
- Aspirin
- Vitamin E supplementation: in HDL dysfunction due to haptoglobin 2-2 genotype
- Metformin or thiazolidinedione derivatives

Thiazolidinediones and niacin have antioxidant effects beyond increasing HDL-C levels. Extended-release *niacin* treatment improved endothelial-protective functions of HDL in diabetic patients [4]. Aspirin, the well-known anti-inflammatory agent, should be tested in moderate doses in subjects with HDL dysfunction and might prove beneficial.

Metformin (850 mg twice a day) at 12 months was shown to decrease serum CRP by a significant 14% in women with IGT compared with the placebo group [88]. The reduction did not reach significance in men.

5.3. Further research needed

On the one hand, further delineation is required of characteristics that define biochemical HDL dysfunction beyond those already developed by Ansell et al [9], Castellani et al [10], Navab et al [63], and Kontush and Chapman [64]. On the other hand, prospective epidemiologic assessment of HDL and its apolipoproteins in cardiometabolic risk will likely be fruitful, particularly in populations with a high prevalence of abdominal obesity such as Middle Eastern, South Asian [85], or Mexican people. Similar population-based studies are needed worldwide in subjects with glucose intolerance. The sex difference in the inflammation-modulated HDL activities warrants further investigation of the hormonal mechanisms, as does the favorable influence of chronic cigarette smoking on the development of diabetes. Finally, further research is needed to improve the function of HDL particles using cholesteryl ester transfer protein (CTEP) inhibitors, niacin, recombinant HDL or apo-mimetic peptides [65].

6. Conclusions

Verified dysfunction of HDL particles isolated especially from diabetic subjects is established. Recent population-based studies revealed dysfunction of HDL or apo A-I circulating in high concentrations in individuals with diabetes or CHD. This process has newly been observed even in a general population, firstly among Turkish adults. These lipoproteins displayed biological evidence of functional defectiveness in terms of unanticipated correlations with inflammatory biomarkers, manifested with the consequence of lack of protection against diabetes and CHD and huge excess in diabetes and CHD incidence in the population. Although HDL dysfunctionality is closely linked to obesity and to inflammation, it seems to be partly independent of these. It is considered that other ethnicities in South Asia, East Europe, and the Middle East may harbor HDL dysfunction in the population at large, whereas only groups with IGT or otherwise at cardiometabolic risk in East Asian and Western populations are likely affected by the stated disorder. The inherent large public health impact demands clinical recognition and institution of appropriate preventive measures as well as the delineation of management that may well include anti-inflammatory drugs.

Acknowledgment

We thank the several pharmaceutical companies in Istanbul, Turkey, that have supported the Turkish Adult Risk Factor survey over the years. The partial logistic support of the Turkish Ministry of Health is acknowledged. We gratefully acknowledge the statistical assistance of Dr Günay Can and appreciate the dedicated works of various coworkers in the survey teams.

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