Dysfunction of high-density lipoprotein and its apolipoproteins: New mechanisms underlying cardiometabolic risk in the population at large

Yüksek yoğunluklu lipoprotein ile apoproteinlerinin işlev kusuru: Erişkin popülasyonda kardiyometabolik riskin altında yatan yeni mekanizmalar

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Summary– We review the metabolic and residual cardiovascular risk existing in populations with prevailing metabolic syndrome (MetS) or in people prone to impaired glucose tolerance. Evidence is presented that enhanced systemic inflammation, or oxidative stress associated with elevated plasma triglyceride-rich lipoproteins and their remnants, and excess oxidized lipoprotein(a) phospholipids underlie this risk. The adverse risk profile is augmented by loss of the anti-inflammatory, anti-oxidative and atheroprotective properties of high-density lipoprotein and its apolipoproteins (apo). Common clinical manifestations are atherogenic dyslipidemia and hypertriglyceridemia with elevated apoB or hypertriglyceridemic waist phenotype. These manifestations are often accompanied by such inflammatory mediators/markers as elevated serum apoE, C-reactive protein, complement C3, and uric acid levels. Compared with men, peri- and postmenopausal women are more commonly and more strongly affected by multiple inflammation mediators. The long-term effects of cigarette smoking are not adverse in such women, but instead, serve as protection against obesity and other health issues. ApoA-I may become dysfunctional in either gender, even in the absence of MetS and diabetes. The public health implications of this cardiometabolic risk are huge. Much research is needed on this topic to further clarify the impact of apoA-I dysfunction, to elucidate the underlying genetics and mechanisms, and to determine preventive measures and optimal management. Avoiding (abdominal) obesity via lifestyle modifications, including dietary changes, improving physical inactivity, and limiting smoking and alcohol consumption, are mainstay measures in the prevention and management of pro-inflammatory states and HDL dysfunction. Omega-3 fatty acids are a good adjunct to lower plasma triglycerides. When further treatment is needed, extended-release niacin or fibrates, with or without statins, are the best options.

Özet– Bu yazıda, metabolik sendromun (MetS) yaygın olduğu ve glukoz tolerans bozukluğuna yatkın popülasyonlarda hakim olan metabolizma ve kalan kalp-damar hastalıkları riski gözden geçirildi. Bu riskin altında, kanda trigliseridden zengin lipoproteinler ile kalıntılarının ve okside olmuş lipoprotein(a) fosfolipidleri fazlalığıyla ilişkili artmış sistemik enflamasyon/oksidatif stres'in yattığına dair kanıtlar sunulmaktadır. Yüksek risk profili, yüksek-yoğunluklu lipoprotein (HDL) ve apolipoproteinlerinin (apo) yangı ve oksidasyona karşı gelen ve aterozdan koruyucu özelliklerinin kaybolmasıyla daha artmaktadır. Sık görülen klinik belirtiler aterojen dislipidemi, artmış apo B'li hipertrigliseridemi veya hipertrigliseridemik bel fenotipi olup, çoğu kez serumda artmış apo E, C-reaktif protein, kompleman C3 ve ürik asit düzeyleri gibi yangı mediyatör/markörleri ile eşlik eder. Erkeklere kıyasla, menopoz çevresi ve sonrasındaki kadınlar bu durumdan daha sık ve daha güçlü biçimde etkilenip çok sayıda yangı belirteci etkin olur. Sigara içiciliğinin uzun süreli etkisi anılan kadınlarda, şişmanlıktan koruma ve diğer mekanizmalar aracılığıyla zararlı değildir. Apo A-I disfonksiyonu her iki cinsiyette MetS ve tip 2 diyabet yokluğunda da gelişebilir. Anılan kardiyometabolik riskin halk sağlığı açısından sonuçları devasadır. Bu alana ilişkin etkiyi, genetiği, makanizmaları koruma ve tedaviyi daha aydınlığa kavuşturmak üzere, çok daha fazla araştırmaya gereksinim vardır. Diyet yoluyla (abdominal) obeziteden korunma, fiziksel hareketsizliği düzeltme ve sigara içiciliği ile alkol tüketimini sınırlamayı içeren hayat tarzı değişiklikleri, yangı durumu ile HDL disfonksiyonunu önleme ve tedavi etmenin temel taşlarıdır. Kanda trigliserid yüksekliğini azaltma amacıyla, omega 3 yağ asitleri uygulamak iyi bir ek önlemdir. Ek ilaç gerekirse, statinlerle birlikte veya birlikte olmayarak, uzun salınımlı niasin veya fibratlar uygulamada en uygun seçenek görünmektedir.

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Traditional cardiovascular risk factors, led by hyperlipidemia, have been responsible for at least one-half of cases of coronary heart disease (CHD).[1] Successful reduction of low-density lipoprotein cholesterol (LDL-C) using statin drugs has reduced the risk of cardiovascular morbidity and mortality.[2] The prevalence of major risk factors, excepting diabetes, (high cholesterol, high blood pressure and smoking) has decreased across all body mass index (BMI) groups in the United States in the last two decades.[3] Yet, the number of deaths from heart disease remained essentially stable over the same period,[4] likely due to an explosive increase in the prevalence of obesity and type-2 diabetes. The recommendations of Adult Treatment Panel-III of the NCEP, and the subsequent modifications by the NHLBI/AHA,[5] delineated as a main treatment target, alternative to LDL-C, non-high-density lipoprotein (non-HDL) cholesterol, which comprises very-low-density (VLDL) and intermediate density lipoproteins. Triglyceride-rich lipoproteins and their remnants have been regarded as causal mechanisms in patients at high risk for cardiovascular disease by a European Atherosclerosis Society consensus panel.[6] The notion of residual vascular risk in dyslipidemic patients was developed based on emerging cardiovascular risk factors such as elevated apolipoprotein (apo) C-III.[7]

Abbreviations:

Apo	*Apolipoprotein*
BMI	*Body mass index*
CHD	*Coronary heart disease*
CRP	*C-reactive protein*
DM	*Diabetes mellitus*
HDL	*High-density lipoprotein*
HtgW	*Hypertriglyceridemic waist*
IGT	*Impaired glucose tolerance*
LDL-C	*Low-density lipoprotein cholesterol*
Lp	*Lipoprotein*
PLTP	*Phospholipid transfer protein*
VLDL	*Very-low-density*

Beyond oxidized LDL, which is the main cause of (inflammatory) atherosclerosis, factors such as lipoprotein[Lp](a), oxidized phospholipids,[8] and adipokines (tumor-necrosis factor-α, interleukin-6, C-reactive protein [CRP]) initiate or propagate inflammatory processes that lead to vascular events. The pro-inflammatory state is counteracted by various enzymes, by the body's antioxidative defense system formed by HDL, and by apolipoproteins, such as apoA-I, and to a lesser extent, apoA-II and apoC-III, occurring in HDL, adiponectin, and others. When the function of this system is impaired, subclinical low-grade inflammation may persist, leading to clinical disorders, such as diabetes mellitus (DM) or CHD.

This review aims to present the increasing evidence that the impaired function of HDL and its apoA-I is a major factor underlying CHD in the general adult population and in some population subsets, a concept that has not been widely recognized thus far. Certain emerging risk variables, such as remnant lipoproteins, Lp(a), oxidized phospholipids, complement C3, apoE, creatinine, and Lp-associated phospholipase ($Lp\text{-}PLA_2$) that are involved in such processes will also be addressed.

Biochemical and epidemiological evidence of HDL dysfunction

HDL is a bioactive particle containing acute phase response proteins, protease inhibitors and complement regulatory proteins.[9,10] Low HDL-C levels are associated with increased CHD risk, but high levels are not uniformly atheroprotective. By assaying the anti-inflammatory activity of HDL, the protective effect of HDL against LDL oxidation was shown to be lost in aortic wall cell cultures in a milieu of inflammation.[9,11] Co-culture assays from patients with coronary artery disease were found to have high concentrations of HDL and to possess less anti-inflammatory activity than healthy controls, suggesting dysfunctional HDL.[12]

HDL protein composition alterations and oxidative damage are thought to impair the atheroprotective properties of HDL. Using mass spectrometry and pattern recognition analysis, Vaisar et al.[13] found that HDL_2 of patients with coronary artery disease contained oxidized methionine residues of apoA-I and elevated levels of apoC-III and concluded that protein oxidation helped generate dysfunctional HDL.

HDL and apoA-I dysfunction in individuals with diabetes and CHD

Non-enzymatic glycation of HDL-associated enzymes, and especially of apoA-I, in diabetic patients depends on glucose concentration and has been shown to increase in the presence of phospholipids.[14] Factors attributed to the deficient anti-inflammatory properties of HDL in diabetic patients include HDL enrichment with conformational alterations of apoA-I; glycation of apolipoproteins and/or HDL-associated enzymes; and oxidative modification of HDL lipids, apolipoproteins and/or enzymes.[15,16]

Evidence from clinical trials and epidemiological studies that elevated levels of HDL and its apolipoproteins may not protect against cardiometabolic risk

Based on previous knowledge, the NCEP Adult Treatment Panel-III attributed a 1 mg/dl (0.026 mmol/L) increase in HDL cholesterol level with a 2-3% decrease in the multi-adjusted risk of CHD. HDL cholesterol concentrations in excess of 60 mg/dl (1.55 mmol/L) counteract 1 risk factor.[17] Yet, several epidemiological studies and clinical trials have had contradictory results. Reports exist documenting HDL dysfunction in subjects with, or at high risk for, CHD,[12,18] or with recurrent cardiovascular events.[19] Very high serum HDL cholesterol levels (>70 mg/dl) and the largest HDL particle size categories were positively associated with cardiovascular risk.[18] High HDL cholesterol did not protect against coronary artery disease when associated with both cholesteryl ester transfer protein and hepatic lipase gene variants in the REGRESS study.[20] Moreover, a recent systematic review of 108 randomized trials involving 299,310 participants disclosed that no association existed between treatment-induced change in HDL cholesterol levels and risk ratios for cardiovascular disease, morbidity and mortality, when changes in LDL cholesterol were adjusted for.[21]

The presence of pro-inflammatory HDL has also been a notable finding in patients with rheumatic diseases, potentially predisposing them to atherosclerosis; in 45% of patients with systemic lupus erythematosus, contrasted to 4% of controls; and in 20% of rheumatoid arthritis patients.[22] The ability of each patient's HDL to prevent oxidation of normal LDL was measured, and oxidized LDL levels were positively correlated with pro-inflammatory HDL levels. Evidence of accelerated atherosclerosis was reported in such chronic inflammatory states, demonstrating the effects of pro-inflammatory HDL.[23]

Male and female residents of Tehran reportedly have low levels of serum HDL cholesterol,[24] similar to Turks. It is worth emphasizing that, in prospective analyses, HDL cholesterol did not significantly predict newly developing cardiovascular disease in diabetic men or women, or in non-diabetic females.[24] Strikingly, CHD risk was nearly two-fold higher in women than in men.

In Israelis, HDL dysfunction, secondary to the haptoglobin 2-2 genotype, has been described.[25] Haptoglobin binds hemoglobin to apoA-I and contains the powerful oxidant heme iron. Hemoglobin and lipid peroxidase levels in HDL were elevated, and HDL function was impaired in diabetic Israeli subjects, indicating that the pro-oxidant hemoglobin converted HDL to a pro-oxidant structure.[25] Haptoglobin and apoA-I are thought to inhibit the activities of lecithin-cholesterol acyltransferase and phospholipid transfer protein (PLTP), thus reducing reverse cholesterol transport.[26] This type of HDL dysfunction could be improved by supplementing treatment with vitamin E.[26]

Evidence of HDL dysfunction in Western populations was clearly demonstrated in Scandinavians with impaired glucose tolerance (IGT).[27] In a 10-year follow-up study of over 9000 subjects without a history of diabetes, HDL-C was found to have a HR of around 1 in subjects with pre-diabetes (IGT and impaired fasting glucose), diverging from both those with normoglycemia and newly-developed diabetes.

Additional findings, primarily from the population-based TARF cohort

HDL particle dysfunction and implications for algorithms

Diverse outcome studies of the TARF cohort disclosed that higher concentrations of HDL cholesterol may not be atheroprotective even in the population at large.[28-30] HDL cholesterol 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]), independently of circulating CRP. In women, HDL cholesterol levels were absolutely not associated with incident CHD.

These important findings were translated into an algorithm for CHD among Turks, women differing in regard to several cardiovascular risk factors[31] from the Framingham algorithm for women. Table 1 discloses that three major risk factors (LDL-C, HDL-C and smoking) were of little or no relevance to Turkish women who were of menopausal age, had diabetes and high CRP levels, and also had high systolic BP.

An analogous assortment of risk factors also manifested from an algorithm derived for type-2 diabetes among Turks. The eight-year risk of DM was esti-

Table 1. Algorithm for incident CHD risk prediction among Turkish men and women aged 30-74 years[31]

Risk factor	Category	Men	Women
Age group (year)	40-49	4	4
	50-59	5	8
	≥60	8	10
Presence of diabetes	Yes	2	3
LDL cholesterol (mg/dL)	≥130	2	1
Systolic BP (mmHg)	120-139	1	2
	140-159	2	2
	≥160	4	4
Current vs. non-smoker	Yes	2	0
HDL cholesterol (mg/dL)	≥50/60	0	0
	40-49/50-59	0	0
	<40/<50	2	0
C-reactive protein (mg/L)	M ≥3.0;	2	2
	F 0.8-6.3		
	>6.3	2	3

Reference categories receive no points: age 30-39 years, non-diabetic, LDL-C <130 mg/dl, SBP <120 mmHg, non-smoker, HDL-C ≥50/60 mg/dL, CRP <3 in males, <0.8 mg/L in females.

mated for 2261 middle-aged Turkish adults.[32] Cox proportional hazard regression and 15 variables were used to predict DM. Discrimination was assessed using the area under receiver operating characteristics curve (AROC). Height, family income bracket, systolic blood pressure, smoking status, alcohol usage, and HDL cholesterol levels were not predictive of diabetes in multivariable analysis for either sex. Male sex, family history of DM, fasting glucose, and waist circumference were predictors. Age and non-HDL cholesterol were also predictors for men, as were physical inactivity and serum C-reactive protein (CRP) for women.[32] The AROC of the final model was 0.783 in men and 0.772 in women (both $p<0.001$). An algorithm using the seven abovementioned variables was developed separately for each sex. Men and women with risk scores in the top quintile were 20 and 50 times more likely to develop DM, respectively, than those in the bottom quintile, a statistically significant difference. The predictive value of the algorithm was validated in two split samples.[32]

Dysfunction of apoA-I

Tertiles of apoA-I were tested to determine the value of apoA-I in predicting diabetes in a basic model adjusted for sex, age, BMI, and usage of lipid-lowering drugs, as well as, in one tertile, smoking status, CRP and HDL cholesterol levels.[29] Instead of an inverse association corresponding to some degree of protection, the top apoA-I tertile was significantly and independently associated in each model with future risk of diabetes in both men and women, at an RR of 1.7 to 1.9. The mid tertile exhibited an insignificantly elevated RR.

It is noteworthy that apoA-I has recently been reported to combine with LDL (apoAI-LDL) during oxidation; high levels of apoAI-LDL could be used to identify coronary artery disease more accurately than CRP, in a cross-sectional study.[33] Modified apoA-I was compared with non-modified apoA-I in terms of functional and structural features, following treatment with artificial sweeteners and fructose in a human cellular *in vitro* model using macrophages and dermal fibroblasts. Modified apoA-I had lost antioxidant ability and had impaired phospholipid binding ability.[34] ApoA-I is implicated in or influences amyloid formation by other proteins. Oxidation of the methionine residues of apoA-I is a pre-requisite for the *in vitro* aggregation of lipid-free apoA-I, and these aggregates display characteristics of amyloid fibrils.[35] Evidence has demonstrated that amyloid fibril formation by apolipoproteins may play a role in the development and progression of atherosclerosis.[35]

Even in a nearly exclusively Western population sample of middle-aged and elderly adults, the likelihood that intermediate and high apoA-I levels may be highly heterogeneous, comprising well-functioning and dysfunctional apoA-I particles, may be derived from Figure 3 in the meta-analysis by the Emerging Risk Factors Collaboration (ERFC).[36] In 22 prospective studies, involving over 90,000 individuals, apoA-I quintile 2 displayed protection of nearly 20% against CHD risk, compared to the lowest quintile. Yet, above 1.44 g/L (in the three highest quintiles, including both sexes), no significant protective effect was apparent.

Lipoprotein (Lp)(a) is presumably not assayable due to autoimmune complex formation

Several observations obtained in a recent meta-analysis covering over 22,000 vascular disease outcomes in 126,000 subjects of European continental

ancestry,[37] and in other individual studies, suggest that part of the serum Lp(a) is not assayable in plasma under certain circumstances. Reasons include:

i) The inverse correlation of Lp(a) with serum fasting triglycerides[37] may mask a true positive correlation, which under circumstances of oxidative stress may cause consumption of Lp(a) lipoprotein during a slow immune response.

ii) An 11% mean decline in sex- and age-adjusted Lp(a) levels occurs[37] in individuals with diabetes (usually associated with activation of complement pathways).

iii) Lp(a)'s poor, yet positive, association with CRP and moderate association with fibrinogen are consistent with its role as an acute phase reactant.

iv) Positive associations (by a mean 4% and 1%, respectively) between Lp(a) and both HDL cholesterol and apoA-I[37] may well reflect a concomitant process of elevated HDL with elevated pro-inflammatory Lp(a).

v) CHD risk related to Lp(a) was high in people with HDL cholesterol levels <55 mg/dl but was not elevated in those with >55 mg/dl,[37] which suggests the presence of HDL dysfunction, inasmuch as in this subset of subjects, Lp(a) may be consumed in a milieu of hypertriglyceridemia.

vi) Plasma Lp(a) decreases dramatically during the third trimester of pregnancy, a state of oxidative stress, while plasma triglycerides increase.[38]

vii) A shift to lower concentrations of apo(a)-containing lipoproteins was observed; these lipoproteins accumulated when triglyceride levels increased in the postprandial state,[39] or after triglyceride infusion.[40]

viii) The thyroid hormone analogue eprotirome lowers both Lp(a) and fasting triglycerides,[41] supporting a positive correlation between them.

In the TARF study, the question of whether aggregation of Lp(a) to apoA-I underlies HDL dysfunction, increasing the risk of CHD, was addressed in a study of 1509 middle-aged Turkish adults at 4.9-years' follow-up. The plot of Lp(a) concentrations in the study sample compared to expected concentrations disclosed substantially lacking values exceeding 40 mg/dl and excess values <10 mg/dl. Lp(a) concentrations in women were linearly related to complement C3, apoE levels and statin use, but not to age or apoA-I (Onat A, Can G, et al., unpublished observations, 2012). Subjects in the low Lp(a) tertile had high mean triglyceride and apoE levels, but these dropped precipitously in the high tertiles ($p \leq 0.002$). This finding suggests an unexpected fall in Lp(a) in a milieu of high levels of apoE (>4.5 mg/dl) and/or triglycerides (>2.0 mmol/L), consistent with aggregation of Lp(a) to apoA-I in an immune complex, rendering apoA-I atherogenic. ApoA-I, but not Lp(a), significantly predicted incident CHD (HR 1.21) in Cox regression analyses, after adjustment for conventional risk factors and statin use. ApoA-I also predicted CHD in individuals in whom metabolic syndrome (MetS) was not identified; the HR magnitude was similar to that of conventional risk factors (Onat A, Can G, et al., unpublished observations, 2012). Autoantigen-autoantibody complexes, such as those considered above, are probably not confined to Lp(a)-apoA-I, but may involve the tripeptide creatinine and, perhaps, asymmetric dimethylarginine (ADMA) and ASP (as outlined below).

Dysfunctional apoA-I mediates prehypertension

BMI is a determinant of prehypertension, and prehypertension, compared to normotension, approximately doubles the risk of DM and CHD in women, independent of obesity. However, prehypertension does not confer substantial risk on Turkish men.[42] We found that newly developed prehypertension is partly caused by dysfunctional serum apoA-I in Turkish women, supporting a role for apoA-I in pro-inflammatory endothelial activation. This was explored in a 6.5-year follow-up study of the TARF cohort excluding individuals with hypertension and/or prehypertension at baseline examination. Of 2207 male and female adults at baseline, apoA-I levels were highest in the hypertensive group, followed by the prehypertensive group and then by the normotensive group (Onat A, Örnek E, et al., unpublished observations, 2012). After adjustment for confounders in a logistic regression model each waist circumference or triglycerides, prehypertension was predicted independently by apoA-I at RRs of 1.23 or 1.32, respectively. Hence, the pro-inflammatory apoA-I, mediated by apoB, contributed to prehypertension, independent of triglyceridemia.

Yet, apoA-I, albeit displaying a positive association, did not independently predict the development

Table 2. Linear covariates of apoA-I and HDL cholesterol (mg/dl) in adults without diabetes or metabolic syndrome

	Men (n=320)			Women (n=338)		
For ApoA-I (mg/dl)	ß-coeff	SE	*p*	ß-coeff	SE	*p*
Fast. triglycerides,¶ mg/dl 0.16-fold	**-3.6**	1.1	.001	-1.0	1.4	.50
ApoB, 27 mg/dl	**9.8**	1.5	<.001	**6.4**	1.8	<.001
Creatinine, 0.24 mg/dl	0.1	1.5	.94	**4.5**	1.7	.008
R^2 explained	0.125, p<0.001			0.07, p<0.001		
For HDL-C (mg/dl)						
Fast. triglycerides,¶ mg/dl 0.16-fold	**-2.5**	0.5	<.001	-1.3	0.7	.071
ApoB, 27 mg/dl	**2.0**	0.8	.01	0.4	0.9	.64
Creatinine, 0.24 mg/dl	0.7	0.7	.32	**1.8**	0.9	.031
Fasting glucose, 22 mg/dl	**2.1**	0.9	.014	**2.2**	0.8	.006
R^2 explained	0.09, p<0.001			0.05, p<0.003		

*Onat A, et al., unpublished observations, 2012; ¶Log-transformed values.

of hypertension in similar models; rather waist circumference, fasting triglycerides or CRP were the determinants. Presumably, inflammatory processes of greater magnitude were required to induce endothelial dysfunction sufficient to generate hypertension.

Apolipoprotein C-III in HDL, a diabetogenic factor among Turks

Unlike apoC-III transported on LDL, HDL apoC-III is thought to have atheroprotective properties.[43] However, a 4.4-year follow-up study of 802 Turks, both males and females, had contrasting results. High levels of apoC-III, measured by turbidimetric immunoassay, proved to be key in causing diabetes, independently predicting newly developed diabetes with a significant 2.5-fold RR per 1 SD, after adjustment for powerful confounders, including waist circumference and HDL cholesterol, among others.[44] This result poses huge public health implications for Turks. To put this finding in context, serum apoC-III promotes Ca^{2+}-dependent β-cell death in cultured mouse pancreases[45] and induces expression of vascular cell adhesion molecule-1 in vascular endothelial cells. Serum apoC-III also increases adhesion of monocytic cells.[46]

Associations of HDL cholesterol and apolipoproteins with inflammation markers

Serum HDL cholesterol was positively correlated with the acute phase reactant fibrinogen, and only weakly inversely correlated with CRP,[28] potentially biological evidence of HDL functional defectiveness. HDL-C was, furthermore, not correlated with fasting insulin concentrations and only weakly correlated with obesity measures in women, compared to men.

In a multiple linear regression analysis, apoA-I levels were positively associated with the female sex and systolic blood pressure, and tended in females to a positive association with CRP, suggesting acquired pro-inflammatory properties.[29] Further positive associations of apoA-I and HDL-C with apo B, glucose and creatinine were found even among healthy people (with neither MetS, nor diabetes; Table 2).

"Hypertriglyceridemic waist" phenotype, circulating Lp(a) and excess cardiometabolic risk

"Hypertriglyceridemic waist" (HtgW) phenotype is associated with a marked increase in cardiometabolic risk for both sexes. Whether Lp(a) may cause apoA-I to become pro-inflammatory was examined epidemiologically in a study of 1328 Turkish adults, with special reference to the impact of HtgW. We analyzed four groups, formed based on the presence or absence of abdominal obesity and elevated triglycerides (Htg). Compared with the isolated Htg group, women with HtgW had significantly higher apoB and complement C3, and the lowest Lp(a) values. In the HtgW group,

Lp(a) was linearly associated with apoB and, paradoxically, in women, inversely associated with gamma-glutamyltransferase. Lp(a) was inversely predictive of HtgW incidence in women (OR 0.80 [95%CI 0.65; 0.97]), regardless of adjustment for relevant confounders, but not in men (Onat A, Can G, et al., unpublished observations, 2012).

Since preβ-1 HDL indicates increased CHD risk[47] and, in Japanese-American men, apoA-1 failed to predict CHD at higher concentrations of HDL cholesterol,[48] we thought to derive a high apoA-I/HDL-C ratio to potentially reflect apoA-I dysfunction secondary to a greater proportional increase in lipid-poor apoA-I and preβ-1 HDL than HDL-C. The sex-specific 70 percentile cutoff values for the ApoA-I/HDL-C ratio (3.67 in men and 3.38 in women) were selected and assessed based on CHD likelihood.

After adjustment for conventional risk factors, HtgW (OR 2.84) and high apoA-I/HDL-C ratios were significantly and additively associated (OR 1.50) with a composite risk of prevalent and incident CHD. An interaction was documented between high apoA-I and low HDL cholesterol levels in women. Type-2 diabetes was strongly predicted by HtgW, partly mediated in men by a high apoA-I/HDL-C ratio. This study indicated that HtgW is associated with excess inflammatory markers and, paradoxically, is predicted in women by lower circulating Lp(a). A high apoA-I/HDL-C ratio contributes additively to the associated marked increase in cardiometabolic risk. These findings are consistent with the aggregation of apoA-I to the oxidized Lp(a) lipoprotein in milieus of enhanced inflammation in women.

Serum γ-glutamyltransferase

In a 4-year prospective follow-up study of 1667 adults, we examined whether the value of GGT in determining incident cardiometabolic risk is independent of obesity using Cox proportional hazard regression analysis. Male sex, sex-dependent age, alcohol usage, BMI, fasting triglycerides, and CRP were significant linear independent determinants of circulating GGT.[49] A one standard deviation increment in GGT activity significantly predicted, for each sex, incident hypertension (HR 1.20]), as well as, MetS, after adjustment for age, alcohol usage, smoking status, BMI, and menopause. Diabetes demonstrated the strongest independent association with GGT activity (HR 1.3 [95%CI 1.1; 1.5]), whereas GGT activity marginally predicted CHD independent of total bilirubin, but not of BMI. Higher serum total bilirubin levels were protective against CHD risk in women. Hence, elevated serum GGT confers risk of hypertension, MetS and diabetes when combined with a high BMI, but mediates adiposity for CHD risk.

Creatinine, a risk factor for endothelial dysfunction

A recent systematic review found that over most of the range of renal function, related CHD risk was unassociated and non-linear, displaying a J-shaped risk curve and manifesting the lowest CHD risk, not in subjects with a normal GFR, but in those with a mild renal dysfunction (GFR 90-70 ml/min/1.73 m²).[50] We, therefore, studied CHD risk in 2089 participants of the TARF cohort with available creatinine determinations. Quartiles of creatinine were used, and the mean follow-up was 3.4 years.

Serum creatinine was not significantly associated in men in a linear regression analysis with six inflammatory variables. However, apoA-I and Lp(a) were significant positive covariates in women, the latter tending to be negatively associated in women without MetS. Logistic regression analysis for CHD risk demonstrated that the highest creatinine quartile (>1.10 mg/dl) was significantly predictive in men at a 2.5-fold compared with the lowest quartile, after adjustment for established risk factors. In contrast, the risk curve for women was U-shaped, with the top and bottom quartiles displaying significantly higher risk (OR 1.4 [95%CI 1.004; 1.96]) compared to the two intermediate quartiles.

In summary, higher serum creatinine values were strongly and independently associated with CHD risk in men but not in women in whom the risk curve is U-shaped. Underlying this phenomenon may be an association between low creatinine levels in women and the aggregation of dysfunctional apoA-I to Lp(a), whereby the tripeptide creatinine may also be incorporated in the antigen-antibody complex.

ApoA-I dysfunction in people without MetS or diabetes: Low creatinine, an independent cardiovascular risk factor in women

We examined whether evidence of apoA-I dysfunction existed in non-diabetic people without MetS, i.e. in the

Table 3. Factors associated with coronary heart disease in non-diabetic adults without MetS

	Men (46/336†)		Women (41/357†)	
	OR	95% CI	OR	95% CI
Age (11 years)	**1.90**	1.34; 2.69	**2.77**	1.86; 4.10
Creatinine (0.24 mg/dl)	**1.63**	1.14; 2.31	**1.29***	1.001; 1.67
C-reactive protein¶ (3-fold)	0.99	0.80; 1.22	**1.50**	1.19; 1.67
Lipoprotein(a)¶ (3-fold)	0.95	0.78; 1.26	1.22	0.94; 1.59
Apolipoprotein A-I (25 mg/dl)	1.00	0.69; 1.49	0.95	0.67; 1.35

OR: Odds ratio; CI: Confidence interval. ¶Log-transformed values; †Numbers of subjects with CHD/total at risk; *See results section for analysis by quartiles.

virtual absence of chronic enhanced inflammation. Using linear regression, we first analyzed the covariates of apoA-I and HDL cholesterol separately in men and women (n=658), in a model comprised of age, fasting glucose, CRP, Lp(a), apoB, fasting triglycerides, and creatinine. As seen in Table 2, apoA-I was positively associated with apoB in both sexes, inversely associated with triglycerides in men, and positively associated with creatinine in women. HDL cholesterol levels were positively associated with fasting glucose in both sexes, with apoB and triglycerides in men, and with creatinine in women. Models were highly significant for the variances in apoA-I or HDL-C.

Next we performed a logistic regression analysis to test the value of eight risk factors in predicting prevalent and incident CHD. The model summarized in Table 3 included systolic BP, smoking status, non-HDL cholesterol, and apoA-I, all of which were totally unrelated to CHD. Age, serum creatinine and CRP were significantly associated in both sexes, and Lp(a) was borderline significantly associated in women. Creatinine was used in a similar model in quartiles, and the intermediate quartiles (quartiles 2 and 3) served as reference; the OR for women was 1.67 (0.65; 4.32) for Q1 and 2.44 (1.004; 5.94) for Q4. The likelihood of CHD in men increased linearly with increasing quartiles. Findings of the two multiple regression analyses strongly suggested that *a)* creatinine represents a marker or mediator of oxidative stress in apparently healthy middle-aged adults, *b)* whilst the CHD/creatinine risk curve was linear for men, it was J-shaped in women, *c)* apoA-I was not cardioprotective and was associated with apoB, and *d)* Lp(a) in women tended to have a positive association with CHD. These observations supported that the involvement of serum creatinine in an immune complex in women is independent of and precedes the pro-inflammatory states of MetS and diabetes.

Hyperuricemia marks HDL dysfunction and, in men, independently marks a pro-inflammatory state

In 1508 non-diabetic participants, associations of serum uric acid with inflammation biomarkers and protective proteins were analyzed cross-sectionally, and associations with incident CHD were analyzed prospectively, using the Cox proportional hazards regression method. In the absence of MetS, uric acid tertiles distinguished highly significantly increasing categories of three MetS components in each sex: inflammation/oxidation markers, apoB and (inversely) current smoking, but not protective proteins such as HDL, apoA-I, or adiponectin.

Distinctions between uric acid tertiles attenuated in the presence of MetS. In a linear regression model comprised of six variables, fasting triglycerides, male sex, and, in women, gamma-glutamyl transferase and age were identified as significant independent covariates of uric acid levels. Cox analysis for incident CHD was predicted by mid and upper uric acid tertiles in men alone, at significant HRs of 2.7, independent of and in addition to conventional risk factors (Onat A, Can G, et al., unpublished observations, 2012).

In summary, elevated serum uric acid levels in non-diabetic people are a marker for independent HDL dysfunction and, in men, pro-inflammation. CHD risk is independently and strongly predicted

by elevated uric acid levels in non-diabetic men. Its modulation by MetS and female gender reflects effect-dilution in states of enhanced systemic inflammation where numerous inflammatory mediators jointly share imparting risk.

Circulating apoE independently and paradoxically reflects pro-inflammatory properties

ApoE is known to possess anti-inflammatory and atheroprotective properties.[51] In dysbetalipoproteinemia (or type III hyperlipoproteinemia), characterized by homozygosity for the receptor binding-defective form of apoE (e.g. apo E2/E2), markedly elevated triglyceride-rich lipoprotein (TRL) remnants exist that are enriched in cholesterol and apoE.[52] We first showed that apoA-I dysfunction in adult Turkish women was independent of the apoE genotype and apoB levels.[53] We then attempted to determine the independent relationship between serum apoE and atherogenic dyslipidemia, hypertriglyceridemia with elevated apoB (HtgB), and apoA-I dysfunctionality by analyzing serum apoE concentrations cross-sectionally in 1127 middle-aged adults. ApoE concentrations showed log-linear associations with apoB levels, apoA-I levels, and waist circumference, independent of CRP and the homeostatic model assessment (HOMA) index. The likelihood of atherogenic dyslipidemia and of HtgB roughly tripled per 1 SD increment in apoE concentrations, in addition to apoE genotype, HOMA, apoA-I, CRP concentrations, and waist circumference. ApoA-I proved protective against atherogenic dyslipidemia, but appeared to promote HtgB, a finding supporting apoA-I dysfunctionality under the latter circumstance harboring higher apoA-I concentrations than in atherogenic dyslipidemia (Onat A, Can G, et al., unpublished observations, 2012).

ApoE concentrations were, furthermore, significantly associated with MetS for both genders, after adjustment for sex, age, apoB, apoA-I, and CRP. Finally, serum apoE predicted age-adjusted incident CHD, independently of CRP, in women alone (Onat A, Can G, et al., unpublished observations, 2012). We concluded that, in a general population prone to MetS, elevated apoE concentrations, irrespective of apoE genotype, reflect pro-inflammatory properties due to strong linkages to HtgB and atherogenic dyslipidemia. Furthermore, elevated apoE concentrations are associated with MetS and, in women, with CHD. Elevated levels of circulating apoE may mediate lipid antigen presentation to aggregate to apoA-I particles, inducing dysfunctionality.

Complement C3

Complement C3 (C3) is an acute phase reactant produced by the liver, secreted by activated macrophages at inflammation sites and by adipocytes, and has a central role in the immune system.[54] After adjusting for three major MetS components and other confounders, increasing C3 levels were found to predict newly developed MetS in Turkish women, with a relative risk similar in magnitude to a recognized MetS component. This result suggests that elevated C3 is probably part of the MetS cluster in women. In Turkish men, circulating C3 interacts with MetS to confer risk of incident diabetes and CHD.[54,55]

Some available evidence suggests that serum C3 may signal an immune process which promotes the development of dysfunctional apoA-I particles, rendering them diabetogenic and atherogenic. Serum apoE concentrations may mediate this process in subsets of populations prone to MetS or impaired glucose tolerance. Moreover, C3 activation induces production of acylation stimulating protein (ASP), which further contributes to the metabolic phenotype.[54]

Interaction between obesity and smoking in Westerners

The complex interactions between obesity and age, smoking, diabetes, hypertension, and dyslipidemia were underlined by Peeters and coworkers.[56] They investigated the long-term consequences of obesity in adulthood on life expectancy in a study of 3457 Framingham Heart participants. They concluded that obesity in adulthood is associated with a decrease in life expectancy of about seven years in non-smokers of both genders. The normal weight participants in their study mostly consisted of smokers. Based on this fact, one can calculate that, overall, smoking was associated with a decrease in life expectancy of about six years for male smokers and only five years in female smokers, compared to non-smoking persons of normal weight at age 40 years. The authors found a significant interaction between smoking status and the effect of being overweight on mortality. They derived their mortality findings from within sex and smoking status strata. They justly argued against ad-

Table 4. Effect of cigarette smoking in certain populations on certain variables or outcomes

	Men	Women
Western populations		
Obesity[56]	Variable	Few obese, commonly normal weight
Mean life expectancy loss at age 40[56]	6 years from age 80	5 years from age 83
People with pre-diabetes	Not well defined	Not well defined
Effect on development of DM[70]	–	Not adverse in smokers <25 cig.
People with RA and SLE[71,72]	Likely slightly beneficial	Likely slightly beneficial
Turkish adults		
Risk of abdominal obesity[63]	Independent 3-fold protection	Independent 3-fold protection
Visceral fat accumulation[67]	Nil	Declined
Risk of elevated CRP[62]	Augmented	Unchanged
Risk of new hypertension[64]	Declined by 20%	Declined by 20%
Insulin sensitivity[68]	Worsened	Improved
Apolipoprotein C-III level[44]	Declined	Declined
Glomerular filtration rate[66]	Independent posit. correlation	Age-dependent posit. correlation
Asymmetric dimethylarginine[65]	Declined by 20%	Declined by 6%
Complement C3[54,55]	Declined	Declined
Apolipoprotein A-I[29]	Declined by 2 mg/dl	Declined by 2 mg/dl
Risk of new MetS & diabetes[30,69]	Insignificant protection	Independent protection
Risk of coronary heart disease[28,30]	Elevated 1.5-fold	Marginal protection

DM: Diabetes mellitus; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; CRP: C-reactive protein; MetS: Metabolic syndrome.

justing for such factors as hypertension and diabetes, because these were downstream physiologic effects of obesity.[57]

Analysis of secular trends according to BMI categories in US adults[3] showed that hypercholesterolemia, hypertension and smoking prevalence declined within all BMI categories in the past two to three decades. The prevalence of diabetes rose significantly from 5.3% to 8.1%. Diagnosed diabetes rose even among normal-weight adults. Flegal and coworkers[58] stated that, ironically, decreased smoking may have contributed somewhat to increasing obesity. Pharmacological treatment of dyslipidemia and hypertension led, as a net result, to a population that is, paradoxically, more obese, diabetic, arthritic, and medicated, but with lower overall CVD risk.[3,59]

Smoking among Turkish women protects against metabolic disorder and confers no risk for CHD

In a large meta-analysis of circulating CRP in over 160,000 participants,[60] current male smokers had 19% higher CRP levels compared to non-smokers, whereas female current smokers had similar or marginally lower CRP levels. In the MONICA Augsburg study,[61] women also differed from men; no positive associations were found between markers of systemic inflammation and female smokers. The gender difference was more pronounced among Turks. Turkish male smokers had significantly higher CRP concentrations, while smoking women had significantly lower age-adjusted CRP concentrations, compared to their counterparts with no history of smoking.[62]

The reduction of abdominal obesity is one beneficial effect of smoking.[63] We have also documented other benefits, including an independent reduction in the risk of developing hypertension,[64] serum apoC-III concentrations,[44] and ADMA,[65] as well as, a positive correlation with estimated glomerular filtration rate (Table 4).[66] Furthermore, women were observed to modestly benefit from the independent effects of

smoking on serum complement C3,[55] the accumulation of visceral fat,[67] and insulin sensitivity.[68]

The above-stated long-term effects of smoking on Turkish women likely provide partial protection against the development of diabetes.[69] Smoking had a significant "protective" effect against diabetes in both genders and against MetS in women, after adjustment for age, baseline family income bracket and physical activity grade.[69]

In a 12-year follow-up study of 114,000 women in the United States, the age-adjusted relative risk of incident diabetes for smokers of <25 cigarettes daily was significantly reduced compared to women with no smoking history.[70] The relative risk of cigarette smoking for cardiovascular disease, though somewhat increased, was not as high in rheumatoid arthritis patients as in the general population and was assessed as significantly reduced for current smoking.[71,72] In human endothelial culture, nicotine was shown to suppress the production of pro-inflammatory cytokines via nicotinic acetylcholine receptor, expressed by macrophages during inflammation.[73]

Relevant gender differences

Gender plays an important role in several aspects of enhanced low-grade inflammation, as well as, its associations and consequences. Females are more prone to enhanced low-grade inflammation, not only in populations predisposed to MetS, but seemingly also in the U.S. (where women harbor higher CRP concentrations than men).[74] Female gender interacts with the associations of certain inflammatory biomarkers among themselves, tending to exhibit no independence of certain associations because many inflammation mediators are at play, the global effect of which overwhelms the independent emergence of a given individual mediator/marker. A clear interaction also exists between female gender and the effects of smoking (as described above) on pro-inflammatory factors, such as circulating CRP, excess adipose tissue, central fat accumulation, insulin sensitivity, and possibly, Lp(a) concentrations. These interactions, in turn, lead to differences in cardiometabolic risk outcomes.

Hypothesis

In certain populations, or population subsets, pro-inflammation (or oxidative stress) is either a major driver or the most important driver of cardiometabolic risk besides elevated serum oxidized LDL. The pro-inflammatory state may be promoted by remnants of VLDL or chylomicrons,[6] which may constitute the primary underlying reason for excess cardiometabolic risk in individuals with MetS. This situation is aggravated by the associated low levels of HDL cholesterol and/or the secondary impairment of HDL particle function at normal or above-normal HDL concentrations.

Excess oxidized phospholipids of Lp(a) are another potential mechanism, documented among Turks without MetS,[8] which may act directly or indirectly, by undergoing an immunologic reaction with apoA-I, rendering it pro-inflammatory. We hypothesize that a decline in Lp(a) levels may be due to Lp(a) consumption (rendering Lp(a) not immunoassayable) resulting from pro-inflammation/oxidative stress (Fig. 1). The latter may be caused by high apoE concentrations and hypertriglyceridemia. In women, C3 levels inde-

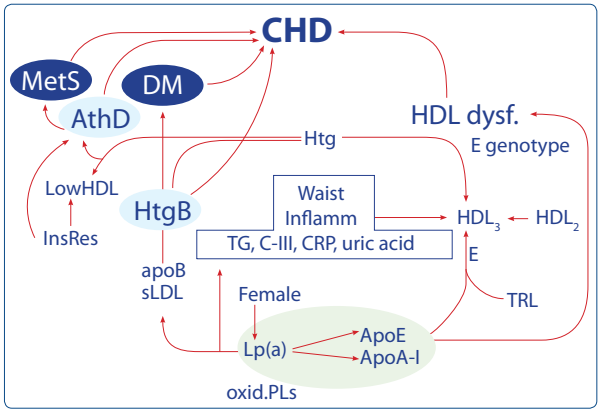

Figure 1. Schematic illustrations of certain mechanisms underlying elevated cardiometabolic risk (MetS, diabetes [DM] and coronary heart disease [CHD]). Pivotal are hypertriglyceridemia (Htg) with the two types of dyslipidemia (atherogenic dyslipidemia, AthD, hypertriglyceridemia with elevated apoB, HtgB) and dysfunction of HDL and apoA-I particles. AthD is mainly affected by insulin resistance and inflammation; HtgB is promoted by the dysfunction of both apoA-I and HDL in women, in combination with elevated apoE and apoB levels. ApoE enrichment in HDL subfractions plays a role in the development of dysfunctional HDL. Enhanced low-grade inflammation, affecting excess oxidized phospholipids associated with elevated lipoprotein[Lp](a) levels, are depicted as determinants. Predominantly in females, low-grade inflammation is aggravated by the binding of anti-inflammatory apolipoproteins A-I and E to [Lp](a) lipoprotein. The pro-inflammatory state is influenced only partly by abdominal obesity, elevated C-reactive protein levels, and the apoE genotype.

Table 5. Outline of the main inflammatory mediators and protective serum proteins with impaired function involved in the development of cardiometabolic risk and, presumably, of related diseases

Inflammatory mediators		Dysfunctional proteins	Outcome
Lipoprotein(a) & oxidized phospholipids		ApoA-I	Prehypertension & hypertension
CRP	Low Lp-PLA$_2$	ApoE	Metabolic syndrome
Hypertriglyceridemia	Fibrinogen	ApoC-III in HDL	Diabetes, type-2
Apolipoprotein B	P-selectin	High-density lipoprotein	Coronary heart disease
Complement C3	ICAM & VCAM	ApoA-II	Ischemic stroke
Hyperuricemia	Platelet activating factor	Adiponectin	Atrial fibrillation
Serum creatinine	Phospholipid TP	*High apoA-I/HDL-C ratio	Rheumatic diseases
γ-glutamyltransferase	Low bilirubin		Psoriasis
ADMA			Odontolysis
Acylation stimulating protein			COPD

CRP: C-reactive protein; ADMA: Asymmetric dimethylarginine; CAM: Cellular adhesion molecules; *70th percentile; Lp-PLA$_2$: Lipoprotein-associated phospholipase A; TP: Transfer protein; COPD: Chronic obstructive pulmonary disease.

pendently contribute to the association between high apoE and Lp(a). Similar immune complexes may also be formed by serum creatinine and apoA-I or apoE (Table 5).

A postulated mechanism, also applicable in inflammatory rheumatic diseases

Available evidence allows us to hypothesize that reduced plasma Lp-PLA$_2$ mass or activity, and diminished hydrolysis of VLDL triglycerides and of Lp(a) phospholipids, may induce a reduction of HDL particles and HDL composition alteration, accompanied by elevated plasma triglycerides. These alterations, in turn, may initiate and contribute to chronic inflammation in subjects with rheumatic diseases, and functional impairment of plasma apoA-I further contributes to chronic inflammation.[72]

Clinical biomarkers of apolipoprotein dysfunction

HDL dysfunction associated with low-grade inflammation is a co-determinant of pre-diabetic states and their progression to diabetes.[75] In seeking clinical biomarkers for impaired function of HDL particles, we analyzed 2725 adults using Cox regression over a follow-up period of 7.3±3.0 years. CRP, C3, triglycerides, and HDL cholesterol were tested for value as predictors of future risk of incident diabetes or CHD. Besides atherogenic dyslipidemia, high-Trg/normal HDL cholesterol was also associated with elevated CRP and diabetes risk in women. The most appropriate markers of impaired anti-inflammatory or atheroprotective HDL function were as follows: in men, a Trg/HDL-C ratio >2 and/or CRP >2.5 mg/L, and in women, Trg >1.7 and C3 >1.3. Thus, in normotriglyceridemic men with normal HDL cholesterol levels, diabetes risk may be elevated due to dysfunctional apoA-I (Onat A, Can G, et al., unpublished observations, 2012).

In addition, elevated serum uric acid levels (>5.2 mg/dl) in non-diabetic men are markers of a pro-inflammatory state and of HDL dysfunction, especially in the absence of MetS (Onat A, Can G, et al., unpublished observations, 2012).

Future research needed

Vast research is needed on the relevance and impact of HDL and apolipoprotein dysfunction (particularly apoA-I, E and C-III) in diverse ethnic groups and in pre-diabetic states. An accurate interpretation of associations with outcome will be necessary in prospective studies. Associations of enhanced pro-inflammatory state/oxidative stress components with cardiometabolic outcomes and HDL dysfunction are needed to better elucidate the role of inflammation mediators (including cellular adhesion molecules, acylation stimulating protein, platelet activation factor, Lp(a) phospholipids, and the Lp-PLA$_2$ enzyme, which we have shown to harbor both atheroprotective and atherogenic properties[76]). The relevance of the immune system and intracellular signaling pathways

in mediating subclinical inflammation and the formation of autoantibodies against inflammation mediators needs to be further delineated. Finally, the various long-term effects of cigarette smoking on women of diverse ethnicities, with or without MetS, need to be investigated objectively, with or without adjusting for BMI, diabetes and hypertension.

Potential prevention and treatment

Dietary strategies to avoid weight gain and lifestyle modification, including increased physical activity and reduced smoking and alcohol consumption, should take precedence in the prevention and management of pro-inflammatory states and HDL dysfunction.

Dietary strategies

Postprandial hyperlipidemia (raised levels of triglycerides, chylomicrons, VLDL, and chylomicron remnants), in addition to postprandial hyperglycemia, induces oxidative stress and inflammation. Ingestion of an excess of high-calorie, easily digestible foods causes abnormal surges in plasma levels of glucose and triglyceride.[77] Post-prandial oxidant stress triggers increases in LDL oxidation, sympathetic tone and thrombogenicity.[77] Studies have demonstrated that diets with a high glycemic index, consisting of low-fiber foods, independently increase the risk of both cardiovascular disease and diabetes.[78]

In the aim of improving postprandial glucose and lipid levels, diets should include large amounts of fresh unprocessed plants, moderate quantities of lean protein and omega-3 fatty acids or monounsaturated fats, and low amounts of carbohydrates, saturated fats and trans fats.[77,78] Minimally processed plants such as vegetables, fruits, nuts, seeds, and grains increase postprandial glucose and triglycerides to a lesser degree than processed foods.[77] Vinegar diminishes post-prandial glycemia, probably because acetic acid slows gastric emptying and, thus, reduces the oxidant stress derived from the meal.[77] Dietary antioxidants from drinks and deeply pigmented plant-based foods, such as berries, cinnamon, red wine, dark chocolate, tea, and pomegranates, help protect the vascular endothelium from postprandial oxidant stress and inflammation.[79] Egg whites, fish, lean meat, including game meat, and poultry breast meat also cause less postprandial inflammation.[80]

Portion control is also of great importance in any diet. The reduction of caloric intake is more effective in improving postprandial oxidative stress by restricting processed carbohydrates, saturated fats and trans fats.[76,79] Even modest weight loss of 5% to 10% decreases postprandial glycemia and lipidemia and reduces the risk of incident diabetes.[80]

Regular moderate alcohol intake, defined as 1-2 drinks/day for women and 2-4 drinks for men, is associated with better life expectancy and with lower risk of CHD in the general population. However, chronic excessive alcohol use has long been known to lead to hypertension, CHD and death.[81] Hence, restriction of alcohol intake is recommended.

Lack of exercise should be avoided to prevent a decrease in insulin sensitivity. A systematic review of the literature found that, in most controlled trials using imaging techniques, overweight or obese patients who engaged in physical activity reported significant reductions in abdominal fat compared with controls.[82]

Although smoking cessation is followed by weight gain in both genders, smoking cessation is critical for better outcomes for men, as the risk of pro-inflammation (revealed by the development of elevated serum CRP) is augmented among smokers. This recommendation is probably also applicable to female smokers who experience an increase in weight or maintain a state of obesity. However, women who do not gain weight while smoking need not be urged to discontinue light to moderate smoking with the ultimate aim of avoiding hazards related to substantial weight gain.

High doses (2-4 g daily) of long chain omega-3 fatty acids, which lower plasma triglycerides by about one-third in individuals with high triglyceride levels, are a good adjunct to a diet.[83] Since cardiovascular outcome studies of non-diabetic people are lacking, evidence of objective benefit is unclear.[84]

Drug therapy for dyslipoproteinemia

In individuals with pro-inflammation and associated HDL dysfunction, dyslipoproteinemia is mainly caused by excess TRL (high levels of fasting or postprandial triglycerides), high Lp(a) levels and low HDL cholesterol levels. Of the available options, niacin and fibrates are the most appropriate treatments, since both influence multiple lipids and lipoproteins.[6,85] Some high-risk patients on statin treatment may need addi-

tional therapy for atherogenic dyslipidemia.[6]

Therapeutic doses of niacin (extended release, ER, 2 g/day) substantially decrease both plasma triglycerides and Lp(a), and increase HDL cholesterol. Niacin may additionally promote beneficial vasoprotective and anti-inflammatory effects independent of lipid modification.[6] Imaging trials have documented the attenuated progression of atherosclerosis and intima-media thickening by niacin. A recent meta-analysis of niacin studies has confirmed its clinical benefits.[86] The impaired vasoprotective effects of HDL in patients with DM were improved after ER niacin therapy.[87] Evidence suggests that niacin better reduces CVD events[88] than fibrates. The risk of incident diabetes induced by niacin in pre-diabetic individuals remains indeterminate.[6] For reducing vasodilation-induced itching, a common side-effect, laropiprant may be a necessary and effective addition. The co-administration of ER niacin with a statin in patients with atherogenic dyslipidemia had a higher efficacy than the statin alone and was generally well-tolerated.[89]

Outcomes from several studies of fibrate therapy alone showed that fibrates reduced nonfatal myocardial infarction but not mortality or fatal myocardial infarction. These studies include the FIELD study, in which fenofibrate was administered to diabetic patients,[90] the older Helsinki Heart study of gemfibrozil,[91] and the BIP trial of bezafibrate.[92] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial[93] demonstrated the safety of using fenofibrate (160 mg daily) with simvastatin; cardiovascular risk was reduced by 31% in a pre-specified diabetic patient subgroup with high triglyceride and low HDL cholesterol levels. A recent meta-analysis of fibrate[94] confirmed the reduction in cardiovascular risk, and suggested a 15% reduction in cardiovascular events per 0.3 mmol/l improvement in the elevated triglyceride levels. Women did not experience any benefit from combination therapy in the ACCORD trial and, hence, caution is required.

Metformin (850 mg b.i.d.) may be used to lower elevated glucose and triglyceride levels. In 12 months, metformin decreased serum CRP levels by a significant 14% in women with impaired glucose tolerance compared to a placebo group; the reduction was not significant in men.[95] Metformin is a structural analog of ADMA and is hypothesized to be an ADMA antagonist, blocking the effect of ADMA as a signaling molecule.[96]

The thyroid hormone analogue eprotirome lowers both Lp(a) and fasting triglyceride levels.[41] Eprotirome might have beneficial effects on some patients in whom both are elevated; these patients should be carefully followed.

In summary, a substantial amount of residual cardiovascular risk exists in population subsets prone to impaired glucose tolerance or even in certain entire adult populations with prevailing MetS. This risk arises from chronic subclinical inflammation/oxidative stress associated with elevated plasma TRLs and their remnants, and likely also from excess oxidized Lp(a) phospholipids. The adverse constellation is seriously compounded by a variable degree of loss of the anti-inflammatory, anti-oxidative and atheroprotective properties of HDL and its apolipoproteins, chiefly of A-I. Clinically, these individuals manifest with hypertriglyceridemic dyslipidemias (atherogenic dyslipidemia and that with elevated apoB), often accompanied by such inflammatory markers as elevated serum apoE, CRP, complement C3, and uric acid levels. Gender impacts this risk profile. Females are more frequently and more strongly affected by multiple inflammation mediators, so that, the associations with the risk of the inflammatory markers do not independently emerge. The long-term effect of cigarette smoking on the pro-inflammatory state is not negative in women, as smoking reduces weight gain and positively affects other factors. Notably, apoA-I dysfunction may occur in either gender in the absence of MetS and type-2 diabetes. ApoA-I dysfunction leads to cardiometabolic risk, a finding which has huge public health implications, given the large number of middle-aged and elderly adults in certain populations and population subsets with dysfunctional apoA-I. Much research is required to further clarify the impact of apoA-I dysfunction, to elucidate the underlying genetics and mechanisms, and to determine preventive measures and optimal management. Dietary strategies to avoid obesity and lifestyle modification to increase exercise and limit smoking and alcohol consumption should precede other measures in the prevention and management of pro-inflammation and HDL dysfunction. Omega-3 fatty acids lower plasma triglycerides, and thus, are a good adjunct to any diet. When these measures are inadequate, ER niacin or fibrates are the

most appropriate drugs to administer with or without statins.

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Key words: Apolipoproteins; cardiometabolic risk; cholesterol, LDL blood; coronary disease; diabetes mellitus; high-density lipoprotein; hypertriglyceridemias; metabolic syndrome; smoking.

Anahtar sözcükler: Apolipoprotein; kardiyometabolik risk; kolesterol, LDL kan; koroner hastalığı; diabetes mellitus; yüksek yoğunluklu lipoprotein; hipertrigliseridemi; metabolik sendrom; sigara içme.