Major influence of dysfunctions of protective serum proteins on cardiometabolic risk among Turks and gender difference

Halkımızda koruyucu protein disfonksiyonlarını kardiyometabolik risk üzerine büyük etkisi ve cinsiyet farkı

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Türk yetişkinlerinde koroner kalp hastalığı (KKH) morbidite ve mortalitesinin diğer toplumlardan farklı biçimde yüksek olduğuna ilişkin TEKHARF Çalışması bilgisi, yakın zamanda daha güçlü biçimde doğrulanmıştır. Bu derlemede, anılan gözlemin altında yatan kandaki koruyucu proteinlerin işlevlerini yitirmesinin, hatta proenflamatuvar ve aterojen niteliklere bürünmesi olayının, toplumumuzda metabolik sendrom (MetS) yaygınlığına eşlik eden dislipidemi, oksidatif süreç ve sistemik yangı sonucuna başlanabileceği üzerinde duruldu. Koruyucu işlevlerinde bozukluk gözlemlenen proteinler yüksek yoğunluklu lipoprotein (HDL) parçacıkları ile, bunun üzerinde yer alan apolipoprotein (apo) A-I, A-II ve C-III, ayrıca, adiponektin olup dünyada ilk kez genel nüfusta tarif edilmektedir. MetS, tip 2 diyabet ve KKH'den oluşan kardiyometabolik riskte, kanda C-reaktif protein (CRP), apoB, apoC-III, fibrinojen yüksekliği ve adiponektin düşüklüğü gibi yangı göstergelerinin rolü, bunların MetS'e dair ATP-III tanımından bağımsızlık oranı ve bunda cinsiyet farklılığı TEKHARF Çalışması'ndan çıkan yayınlara dayanarak açıklanmaktadır. Üstelik, adiponektin disfonksiyonu ve HDL parçacıkları ile ilgili proteinlerin koruyuculuk bozukluklarının halkımızda kardiyometabolik riski büyük ölçüde artırdığı, KKH riskini yetişkinlerimizin yarısında geleneksel risk faktörleri kadar veya daha fazla yükselttiği bildirilmektedir. Sigara içiciliğinin Türk kadınlarında, başta CRP olmak üzere, disfonksiyonlu apoA-I ve viseral yağ birikimi üzerine olumlu etkileri aracılığıyla, hipertansiyon, MetS ve diyabet gelişmesini azalttığının altı çizilmektedir. Olağanüstü önemi içeren bu bilgiler, orta yaşlı Türk yetişkinlerinde kalp-damar sağlığına ilişkin önlem ve tedavi stratejilerinde köklü değişikliklere hızla gidilmesi yolunda ilgili ve yetkililere ışık tutmaktadır.

Anahtar sözcükler: Apolipoprotein; kolesterol, HDL; koroner hastalık; enflamasyon; risk faktörü; cinsiyet faktörü; sigara içme.

Knowledge obtained from the Turkish Adult Risk Factor (TARF) study on higher morbidity and mortality rates compared to other populations, from coronary heart disease (CHD) among Turkish adults has been confirmed more strongly recently. This review provides insight that the dysfunctions of protective serum proteins, attaining pro-inflammatory and atherogenic features, may be attributed to atherogenic dyslipidemia, oxidative stress, and systemic inflammation associated with the high prevalence of metabolic syndrome (MetS) among Turks. The mentioned protective protein dysfunctions, firstly described in a general population to date, are high-density lipoprotein (HDL), apolipoprotein (apo) A-I, A-II, and apoC-III, apart from adiponectin. Based on published findings of the TARF study, this review discusses the role of inflammatory mediators such as elevated C-reactive protein (CRP), apoB, apoC-III, fibrinogen, and low adiponectin serum levels on cardiometabolic risks comprising MetS, type 2 diabetes, and CHD, the degree of independence of these mediators from the ATP-III-defined MetS, and the influence of sex. Moreover, it is emphasized that dysfunctions of adiponectin and protective proteins related to HDL particles increase not only cardiometabolic risk significantly but also CHD risk among half of Turkish adults in a magnitude similar to or greater than that associated with traditional risk factors. Also underlined is the observation that cigarette smoking reduces the risk in Turkish women for the development of hypertension, MetS, and diabetes by mediation of positive effects on dysfunctional apoA-I, visceral fat accumulation and, above all, CRP levels. This knowledge is of utmost importance and sheds light to authorities and those concerned on the necessity of urgent and radical modifications regarding strategies in prevention and management of cardiovascular health of middle-aged Turks.

Key words: Apolipoproteins; cholesterol, HDL; coronary disease; inflammation; risk factors; sex factors; smoking.

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Observations from the Turkish Adult Risk Factor (TARF) Study have underlined the fact that metabolic syndrome (MetS) defined as an inflammatory condition and not included among the constituents of ATP-III exhibits marked differences between Turkish men and women in terms of structure of the syndrome and the risks of diabetes and coronary heart disease. The widely used definition of ATP-III, whether modified or non-modified, does not include inflammation mediators such as C-reactive protein (CRP), apolipoprotein (apo) B and fibrinogen in males. However, these three markers of inflammation are constituents of MetS among Turkish men; and apart from CRP, they act as determinant of type-2 diabetes and coronary heart disease (CHD) by means of MetS. CRP also has an independent effect on cardiometabolic risk.[ ] On the other hand, according to the definition of ATP-III, in addition to these inflammatory mediators MetS also includes the dysfunction of apoA-I and other protective proteins. Despite the effect of CRP and apo-B on diabetes mellitus alone[2] and of fibrinogen[3] and adiponectin dysfunction on the risk of CHD, independent of abdominal obesity, the negative effects on cardiometabolic risk, including protein dysfunction are generally through MetS (Figure 1).

In the aforementioned protein dysfunction, increased ratio of apoA-I to HDL-cholesterol in favor of apoA-I may be considered as an indication for increased inflammation. Increase in the level of HDL-cholesterol together with this ratio, during the process of inflammation, leads to the exclusion of individuals who representing MetS from the definition. In conclusion, the effect of concentrations of apo-B[2] and apoA-I in women on increasing systolic blood pressure (BP)[4] sheds light on the gender-related inflammation-MetS relationship.

Gender and the relationship between inflammatory mediators and MetS

The definition of MetS ATP-III has been modified to meet the AHA/NHLBI prediabetic threshold of 100 mg/dl.[5] We are using the MetS definition by adding an approximated Turkish male waist circumference of 95 cm.[6] The determining nature of plasma fibrinogen on MetS was investigated during a follow-up period of 6.6 years on a total of 2234 men and women with a mean age of 49±12 at baseline.[7] Individuals with MetS at baseline were excluded from the investigation. Fibrinogen levels did not act as a predictor of MetS in any of the models in women; however, even the regression model in men which involved age, cigarette smoking and the five components of MetS with an equivalent relative risk of 1.10 [95% CI, 0.99-1.24] for every 1 g/l increased level. In another analysis increased fibrinogen levels was not found to act as an independent predictor of waist circumference.[7] This demonstrates that fibrinogen acts as an inflammatory factor for the determination of MetS in men, independent of central obesity in men.

However, plasma fibrinogen demonstrated an independent significance for the prediction of CHD in women (RR 1.40; 95% CI, 1.18-1.66 against an increase by 1 g/l), whereas in men CHD could not be predicted independently by the components of MetS.[3]

The relationship of serum CRP with MetS was investigated in a prospective study involving 2590 individuals during a mean follow up period of 4.3 years.[1] The baseline concentrations of CRP acted as a predictor of newly developed MetS for both genders with a hazard ratio of 1.16 (95% CI 1.02-1.32), similar to its independent predictor nature of atherogenic dyslipidemia and hypertension. The CRP level also predicted the progression of prediabetes (fasting plasma glucose >100 mg/dl) to diabetes in women, but not in men, with a hazard ratio of 1.39 (95% CI, 1.21-1.59). It is also important to consider prediction of CHD: CRP also contributed significantly to the seven established risk factors including waist circumference, with a 1.18-fold hazard ratio. As a consequence, CRP was considered as a significant predictor for cardiometabolic risk in Turkish adults and as a result also considered to represent an additional risk factor for the constituents of MetS, a risk which is affected by female gender, cigarette smoking and apo B levels.

The relationship of serum apo B levels with MetS was also investigated in yet another prospective study on 2348 individuals during a mean follow up period of 5.9 years.[2] Apo B concentrations were divided into three segments separated by margins of 120 and 95 mg/dl. In the logistic analysis, the upper segment predicted the development of MetS - independent of waist circumference, CRP, physical activity and family income - with a 2-fold relative risk in both genders ($p<0.02$) and approximately a 3-fold relative risk for atherogenic dyslipidemia ($p=0.001$), compared to the lower segment. In women, the upper one third of serum apo B also independently predicted hypertension (RR 1.71; 95% CI 1.001-2.92), and also diabetes together with waist circumference. In other words, concentrations of apo B which expresses small LDL cholesterol particles is a significant predictor for cardiometabolic risk, independent of waist circumference and CRP, in adults who are know to demonstrate a greater incidence of MetS. The relationship of CRP and apo B concentrations with diabetes mellitus is independent of abdominal obesity in women.

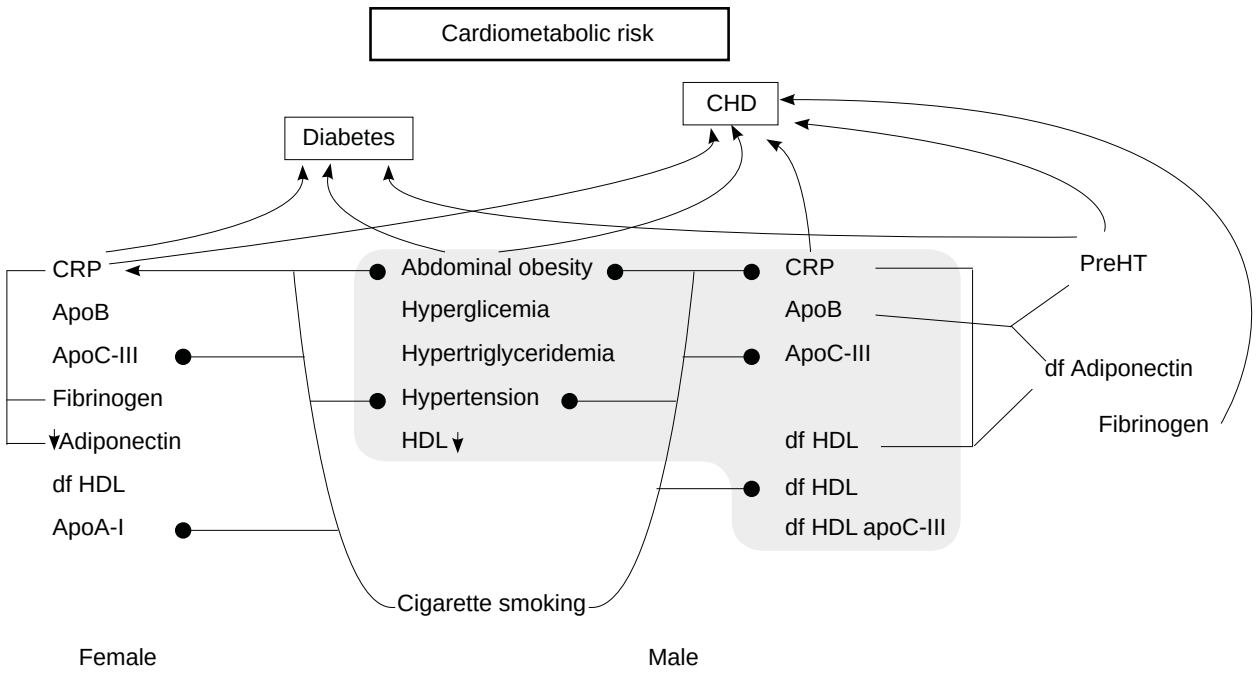

Figure 1. Diagram showing prognosis of metabolic syndrome (MetS) and cardiometabolic risk of diabetes and coronary heart disease (CHD). In addition to ATP-III components, there is an independent relationship of Mets with inflammatory factors and serum protein dysfunctions, indicating an effect on cardiometabolic risk. Cigarette smoking has also some effects on several factors, while gender difference is stressed (●–decreasing effect, ➝ increasing effect). Prehypertension (Pre-HT) leads to diabetes and CHD, resulting in an interaction with ApoB adiponectin dysfunction.

The relationship of adiponectin dysfunction with cardiometabolic risk is described below.

Gender and relationship of protective protein dysfunction with diabetes mellitus and MetS

Small or great disappearance of the ability for protection from cardiometabolic risk, or even acquiring diabetogenic or atherogenic qualities in Turkish adults has so far been demonstrated only in the TARF study. The proteins mentioned, especially small HDL and apoA-I, are A-II and apoC-III[4] (Onat A et al. Serum apolipoprotein C-III in HDL: a key diabetogenic risk factor among Turks [It is considered in Diabet Med.]).

The value of serum apoA-I at baseline was divided into approximately three equal segments using the following limit range in 2111 individuals: ≤1.12 and >1.35 g/l in men, ≤1.25 and >1.50 g/l in women. One third of the segments consisted of 344, 358, 342 men and 361, 346, 360 women.[4] In the multiple regression analysis apoA-I level was found to have a significant relationship with age, gender, alcohol consumption, cigarette smoking (inversely), and with systolic BP (in women). After adjustments for age, body mass index (BMI), CRP, HDL-cholesterol and lipid lowering drugs during a mean follow-up period of 7.4 years, the high apoA-I segment predicted for the development of the risk of diabetes with a relative risk of 1.98 (95% CI; 1.31-3.0). The high apoA-I segment also demonstrated an affinity for a relationship with hypertension and CHD in women. Consequently, it was concluded that the risk of diabetes mellitus in the Turkish population was also increased by apoA-I, in addition to age, BMI, CRP and HDL-cholesterol, and that the systemic inflammation which accompanied MetS could transform apoA-I into inflammatory particles. The association of apoA-I and small LDL-cholesterol may have played a role in this process.

In the linear regression analysis involving nine variables performed in the pilot study which we conducted in 2004 on 193 adults to measure the levels of serum apoA-II during a mean four-year following-up period, the values were found to have a significant relationship with HDL-cholesterol and complement C3; in other words they were found to have pro-inflammatory effects (Onat A et al. Anti-inflammatory dysfunctionality of apolipoprotein A-II levels: a 4-year follow-up study in an elderly Turkish sample [Not yet published]). In the logistic regression analysis, after making adjustments for HDL-cholesterol with some of the other variable, the high values (>30/>33 mg/dl) were shown to predict for incident MetS and type 2 diabetes mellitus in both genders compared to the lower

Tablo 1. Protective effect of HDL-C against several diseases in Turkish men and women

	Men	Women
Coronary heart disease	Significantly protective	No protection
Type 2 diabetes	No protection	Protective for 40-60 mg/dL
Death event	No protection	Protective for 40-60 mg/dL

values, with a relative risk of more than three, instead of 1 SD increase. No significant function of apoA-II values was observed for prevalent and incident CHD. In summary, serum apoA-II concentrations were also shown to possess inflammatory protective dysfunction, similar to other proteins associated with HDL particles. This finding contributes to the excessive cardiometabolic risk observed in the Turkish population.

In a study conducted in 2001 we investigated the effect of lipoprotein-loaded apoC-III, another apoprotein rich in both HDL and triglycerides, on cardiometabolic risk during a mean follow-up 4.4-year period. In a total of 802 individuals both fractions of total apoC-III were found to have a linear relationship with alcohol consumption and an inverse relationship with cigarette smoking. In women it was also found to have a weak relationship with complement C3 and HDL apoC-III and a positive relationship with apoA-I (Onat A, et al. Serum apolipoprotein C-III in HDL: a key diabetogenic risk factor among Turks [It is considered in Diabet Med]).

After excluding the baseline associated diseases and adjusting for gender, age, cigarette smoking, alcohol consumption and lipid lowering drug use in those who were being followed up, total or non-HDL apoC-III was found to predict for newly developed MetS with a hazard ratio of 1.8 (95% CI; 1.35-2.4). Newly developed CHD was also predicted with a hazard ration of 1.33 (95% CI; 1.04-1.70) after adjusting systolic BP for non-HDL apoC-III. This ratio demonstrated a weakened significance at borderline after making additional adjustment for non-HDL cholesterol. HDL (or total) apoC-III also predicted newly developed diabetes mellitus (HR 1.65; 95% CI; 1.27-2.11) after adjustments for waist circumference and HDL cholesterol; and even represented a better predictor than waist circumference (Onat et al).

It can be concluded that serum total apoC-III had a positive relationship with some inflammatory markers and an inverse linear relationship with cigarette smoking. Dysfunctional HDL apoC-III is a stronger predictor of type 2 diabetes mellitus than waist circumference in our adult population. It concluded that non-HDL apoC-III independently acted as a strong predictor for the development of MetS, and acted as a moderate predictor of incident CHD independent of non-lipid factors (Figure 1).

We came across findings which demonstrate that HDL particles with the most protective function in human against atherogenicity and inflammation, also has important dysfunctions in Turkish adults. Findings related to diabetes are presented here whereas those associated with CHD are shown below. Gender was also found to be a determinant in various ways for two target points. The HDL-cholesterol levels at baseline of our 3035 middle-aged adults was interestingly found to have a positive relationship with plasma fibrinogen, and an inverse but negative relationship with CRP. However, no relationship was demonstrated with fasting insulin (Onat et al). From this ascertainment, apart from the decreased protective function of HDL particles in our adults against inflammatory mediators, it is disturbing that it also approaches inflammatory mediators like fibrinogen.

Type 2 diabetes mellitus was monitored for a mean follow up period of 7.8 years on participants who were excluded from the study. HDL-cholesterol concentrations did not protect men against the risk of diabetes. In women, after making adjustments including one-third of apoA-I segment, mid-levels of HDL-cholesterol (40-60 mg/dl) were found to protect against diabetes to almost half (RR 0.57; 95% CI; 0.36-0.90), when compared to lower values. However, values above 60 mg/dl do not significantly protect women, and HDL particles of these values were found to be heterogeneous;[8] it is suggested that women who have lost the inflammatory properties of HDL were also among individuals who maintained these properties (Table 1). In summary, the protective nature of HDL particles against cardiometabolic metabolic risk among Turks is suggested to be partially dysfunctional, and gender is thought to act as a partial determinant for this deficiency. This remarkably important observation suggests a possible chronic subclinical inflammation as the origin. There are strong opinions suggesting that HDL dysfunction may play a role in the increased coronary artery disease among Indians.[9]

Adiponectin which is synthesized by adipocytes has anti-inflammatory, anti-atherogenic and insulin sensitivity effects. There has been conflicting reports concerning protection against coronary diseases in humans. In the

cross-sectional analysis of serum total adiponectin conducted on 1200 individuals by the ELISA method, adiponectin was found to maintain its effect of on insulin sensitivity, paralleled with a decrease in obesity measurements. In the multivariate linear regression analysis, insulin and sex hormone binding globulin (SHBG) were found to be significantly related with waist circumference (or BMI), whereas no relationship was demonstrated with adiponectin.[10] adiponectin was found to be related with insulin and SHBG, but not with BMI, in the multivariate linear regression analysis. In men, HDL-cholesterol or CRP were covariants of adiponectin; however, in women adiponectin was found to have a relationship independent of SHBG, BMI and insulin levels, but not with these parameters. In summary, obesity in Turkish adults is said to have a conflicting relationship with adiponectin levels. On the other hand, serum adiponectin was found to have a relationship with inflammatory mediators and HDL-cholesterol only in men, independent of obesity and hyperinsulinemia. In women, inflammatory activities were found to have weakened by the effect of SHBG.

We demonstrated that high adiponectin values protected women from diabetes and hypertension, independent of obesity. However, these high values did not protect Turkish men.[11] In our gender specific evaluation we divided adiponectin values into two equal parts and made adjustments for age with thresholds of 8.3 µg/ml in men and 10.6 µg/ml in women; high adiponectin values in women were found to be significantly related with diabetes (OR 0.55, p=0.01) and hypertension (OR 0.64, p=0.012) in terms of protection, than low values. This was not the case in men. Adjustments for cigarette smoking and the presence of high/low BMI did not change this gender-based relationship. Increase in serum adiponectin is reported to be due to dysfunction of adiponectin degradation in menopausal women.[12]

Low adiponectin levels and high BMI demonstrated a significant interaction in both genders, in the relationship of adiponectin with MetS. Meanwhile, in addition to the five components of MetS, low adiponectin levels were found to have a relationship with MetS only in men.[11] In conclusion, serum adiponectin concentration in association with metabolic dysfunctions is suggested to demonstrate gender differences with regards to protection against cardiometabolic risks due to anti-inflammatory and anti-oxidative dysfunction. Turkish men have diabetes-associated adiponectin dysfunction, independent of obesity. This disorder demonstrates that decreased levels of adiponectin, which has acquired mild inflammatory properties in men, is a MetS component independent of the components of MetS, as expressed above concerning serum fibrinogen. Whereas in women, the upper quarter values of adiponectin which have undergone a major fundamental dysfunctions, and not a decrease in adiponectin, was found to have a relationship with MetS independent of the MetS components (Figure 1).

Gender and the relationship of protective protein dysfunction with CHD

This especially concerns HDL particles and its apoprotein - apoA-I. A total of 3035 middle-aged adults with no CHD at baseline were followed up for a mean duration of 7.8 years. The relative risk of HDL-cholesterol for CHD was 1 SD, in other words, an increase of 12 mg/dl; and after adjustments for age, cigarette smoking, level of physical activity, hypertension, abdominal obesity, diabetes mellitus and use of lipid lowering drugs, it was found to protect men from future CHD (RR 0.80; 95% CI; 0.69-0.95). The degree of protection was similar to the rate obtained from epidemiologic studies and trials conducted on various populations. On the other hand, no sign of a protective effect of HDL-cholesterol was reported in women: the relative risk from the regression analysis including age, cigarette smoking, waist circumference, hypertension and diabetes mellitus was found to be 1.00 (95% CI; 0.99-1.01) (Onat et al).

A probable relationship of the high apoa-I segment with CHD in women[4] has partially been mentioned above. This observation which did not attain a significant level was found to be significant with dyslipidemia including hypertriglyceridemia. ApoA-I was in association with LDL-cholesterol during the oxidation process (apoAI-LDL); and it has recently been reported in a cross-sectional study that it predicted for CHD more than CRP.[13] A similar process may be attributed to that in some of our adults. On the other hand, increased HDL-cholesterol levels have recently been demonstrated in two studies not to protect against cardiovascular diseases - although not in the general population. In two other prospective studies, very high levels (>70 mg/dl) showed a positive relationship with high categories of HDL particles and apoA-I cardiovascular risk.[14] In another publication increased HDL-cholesterol, cholesterol ester transfer protein (CETP) and hepatic lipase gene variants were reported not to protect against coronary artery disease.[15]

ApoA-I, adiponectin and prehypertension in hypertriglyceridemic dyslipidemia

We investigated the relationship of the cardio-

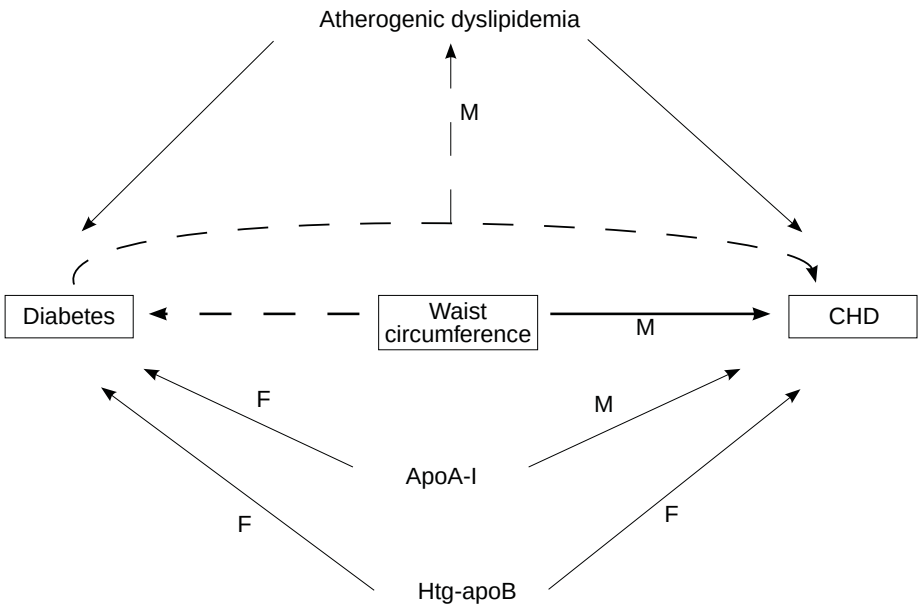

Figure 2. Diagram showing four major risk factors for cardiometabolic risk in Turkish adults. Arrows indicate a significant role for diabetes and coronary heart disease (CHD) in both men and women. M stands for male, while F stands for female. Dotted lines indicate the reason for waist circumference. Women present with cardiometabolic risk of increased apoB and hypertriglyceridemia (Htg-apoB), while waist circumference is an independent indicator of CHD risk. CHD is associated with atherogenic dyslipidemia and apoA-I independent from waist circumference in men. Atherogenic dyslipidemia leads to partially increased waist circumference independent from diabetes risk. All four factors lead to diabetes independently in women, while CHD risk is likely associated with dyslipidemia, but not waist circumference or apoA-I.

metabolic risk of high apoA-I levels with two hypertriglyceridemic dyslipidemia (with low HDL-cholesterol [atherogenic dyslipidemia, AD] or with increased apoB [HTg+B]) cases. The triglyceride values of 2676 individuals determined at baseline were followed up for a mean period of 7.4 years. Although atherogenic dyslipidemia significantly predicted for age-adjusted diabetes and CHD in both genders, HTg+B predicted for these results only in women. Serum adiponectin was reported to protect men in various ways. Although it protected women from diabetes, this was not the case for the risk of CHD. ApoA-I levels predicted for the risk of CHD irrespective of the type of dyslipidemia associated with the model with a hazard ratio of 1.18 (95% CI; 1.03-1.39).

In the analysis including atherogenic dyslipidemia apoA-I was found to predict for diabetes in both genders. However, in analyses including HTg+B, apoA-I was not found to be significant in men, but demonstrated a borderline significance in women (RR 1.006. 95% CI; 1.000-1.012). By so doing, the presence of a triple correlation including increased apoB-adiponectin in women was shown (Figure 1 and 2).

Prehypertension (BP of 120-139/80-90 mmHg) is a condition which interacts to predict for diabetes and the development of CHD in Turkish women, and not in Turkish men (after adjustments for BMI the relative risk for CHD is 1.95; 95% CI; 1.04-3.66).[16] Following our observation that serum adiponectin apo B had a linear relationship only in women (independent of waist circumference and some metabolic parameters)[10], we arrived at the following hypothesis. Adiponectin and small LDL particles resulted in prehypertension through endothelial dysfunction, since it had an interaction only in women. The observation mentioned above partly explains the higher blood pressure in Turkish women compared to the men, contrary to German and other western communities.[17]

In summary, it was demonstrated that the increased cardiometabolic risk by apoA-I levels in Turkish adults was partly independent of hypertriglyceridemic

dyslipidemia. HTg+B was atherogenic only in women with severely dysfunctional anti-atherogenic property of adiponectin. It is demonstrated that a triple correlation including increased apoB-adiponectin in women played a role in the cardiometabolic risk.

The definition of MetS affects apoA-I and HDL-cholesterol dysfunctions

HDL-cholesterol is known to be one of the major five components of metabolic syndrome. In the TARF study HDL-cholesterol is reported to be present in 89% of men and women with MetS, according to the ATP-III definition; according to the TARF definition it was observed in 87% of men and 80% of women.[18] HDL-cholesterol was found to be ≥50 mg/dl in one out of five women according to the definition of MetS. This indicates the presence of a dysfunction of HDL particles for women who met the criteria in relation to the other components. On the other hand, hypertriglyceridemia was found to significantly predict for CHD (with a RR of 1.8) in 2007 women and men with MetS independent of abdominal obesity. However, a HDL-cholesterol decrease (<40/45 mg/dl) was reported.[18] This demonstrates that abdominal obesity, triglyceride, and increased blood pressure were independent predictor of CHD in Turkish adults with MetS; at the HDL-cholesterol level decreased values were not shown to be different from increased values. These explanations concern only individuals diagnosed with MetS; since it is known that HDL-cholesterol protected against CHD in those without MetS (Onat et al). This observation also proves that HDL particles are susceptible for dysfunction during the excessive oxidative process of MetS. On the other hand, it is stressed that consideration of HDL-cholesterol as criteria in the definition would be inaccurate in communities with widespread MetS.

In a community similar to our population with common protective protein dysfunction, apoA-I/HDL-C ratio complicates the definition of MetS and results in syndrome more rapidly even, despite a misconception of its protective effect in both genders.[19] In a logistic regression analysis including 1,601 men and women, subjects were evaluated based on age, cigarette smoking, apoE genotype, apoB and apoA-I. The analysis showed that apoA-I level was not protective against diabetes in men (for 33 mg increase in apoA-I: RR 1.00; 95% CI 0.82; 1.2) and increased the risk in women (RR 1.30; 95% CI 1.04; 1.63), whereas levels significantly prevents the risk of MetS in both genders.[19]

This conflict is derived from the following: even though diabetes is not evaluated as the extent of dyslipidemia, MetS is defined using triglyceride and HDL-C criteria. In subjects without oxidative stress, normal but low HDL-C and apoA-I presenting with moderate or high triglyceride levels refer to an accurate classification of MetS. However, apoA-I dysfunction and HDL-C (with similar dysfunction) may mimic as if MetS is absent, increasing serum triglycerides in patients with oxidative stress. Therefore, while apoA-I concentration may pretend to have a protective effect agains MetS, high triglyceride and apoA-I level may lead to development of diabetes in presence of excessive oxidation. We believe that apoA-I/HDL-C ratio (>3.0/3 mg/dL in women, >3.25/3 in men) is a determinant of MetS and diabetes, continuing our efforts to enlighten this issue.

A consensus on debate whether or not LDL-C is lower in Turkish people

Over a decade ago, the likely nature of having low HDL-C in adults was dominant perception as proposed by Turkish Heart Study[20] and supported by TARF Study.[21] It was significantly associated with inheritance[20] or prevalence of MetS or environmental factors.[21] Many studies including less sample size in the past six years[22,23] revealed that HDL-C level was not lower in Turkish people, emphasizing the need for further studies to confirm or refute this hypothesis.

Several findings are attributed to support the former perception, but not the latter. The latter is more common in patients with hypertension, diabetes, and CHD. The former perception gives more accurate information about public health, whereas the latter presents with higher, but not lower, HDL-C level. Aging population which we are concerned due to the likelihood of dysfunction presenting with higher HDL-C level is also a critical issue.

On the other hand, worrying clinical effect of low HDL-C on public health which has not been eradicated yet presents normal functional heterogeneity in a certain population, alerting us for new precautions.

It would be more appropriate not to rely on high HDL-C concentrations. Cardiometabolic risk evaluation should be performed in consideration of other risk factors. For instance, the analyses which we performed showed that a triglyceride level of >150 mg/dL suggested a high concentration of HDL-C dysfunction. These findings suggest the need for further studies to improve the functions of CETP inhibitors, niacin, recombinant HDL or apomimetic peptides.[24] As a result, underlying hormone mechanisms of gender difference should be thoroughly investigated in inflammation associated HDL activities.

The effect of protective protein dysfunction

In the late 20th century, the TARF study suggested high morbidity and mortality level of CHD in Turkish adults based on two following findings: (i) 6/1000 mortality rate annually in 45-74 years of age, particularly in Europe,[25] and (ii) higher scores of CHD in Framingham risk scale (FRS) than conventional risk factors.[26] The latter was evaluated in the prospective TARF study cohort including 3027 subjects with a 7.24 year follow-up, which was performed 8 years after the first study cohort.

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In the late 20th century, TARF study suggested high morbidity and mortality level of CHD in Turkish adults based on two following findings: (i) 6/1000 mortality rate annually at the age of 45-74 years, particularly in Europe,[25] and (ii) higher scores of CHD in Framingham risk scale (FRS) than conventional risk factors.[26] The latter was evaluated in the prospective TARF study cohort including 3027 subjects with a 7.24 year follow-up, which was performed 8 years after the first study cohort.

Annual rate of CHD development based on risk factors was estimated as 24.7%; however a 2.2 fold increase was seen. Based on Framingham score percentiles according to gender, three of five percentiles at the bottom showed male incidence of CHD, while two of five percentiles at the top increased with a 2-fold increase (Onat A et al. High absolute coronary disease risk among Turks: involvement of risk factors additional to traditional ones [considered in the Int. J. Epidemiol]). The incidence of CHD in two percentiles at the bottom in female, a 2.7-fold increase was seen in three percentiles at the top. Subjects in the high percentiles presented with abdominal obesity and apoA-I dysfunction. Men were also likely to have increased nonHDL-C, total apoC-III, apoB, triglyceride levels and adiponectin dysfunction. On the other hand CRP was an independent indicator of CHD in women. Lack of protective protein in HDL-C, and apoC-III dysfunction were also observed. Increased CHD risk in percentiles was associated with absent factors in Framingham model, central obesity, and related HDL-C, apoC-III, A-I and adiponectin dysfunction (Onat et al.).

The effects of protective protein dysfunction is critical for cardiovascular and metabolic health. While conservative estimations suggest an annual CHD incidence of 240.000 to 150.000 in men and women, respectively, annual incidence of fatal or non-fatal CHD development is 90.000 to 110.000 in men and 70.000 to 90.000 in women. This may be explained by non-conservative risk factors.

Therefore, prevention and treatment strategies should cover more than the followings: prevention and reversion of presence of abdominal obesity in men and general obesity in women, which have been considered so far. While the relationship between cigarette smoking and obesity is perceived differently in Turkish population compared to Western population, anti-smoking campaigns should also address to women, as the obesity has a few times more adverse effect on women except cardiovascular health problems. TARF study evidently showed that cigarette smoking was associated with decreased apoC-III;[27] lower risk of development of abdominal obesity,[6,28] hypertension,[29] MetS and diabetes;[30] beneficial effect on pre-heparin lipoprotein lipase activity,[31] and visceral fat accumulation[32] and decreased CHD non-significantly. Nicotine stimulates angiogenesis in presence of inflammation and ischemia, using endothelial acetylcholinergic receptors and increasing eNOS phosphorylation via Akt which regulates eNOS activity.[33] In addition, a prospective study including non-obese Japannese men showed that cigarette smoking decreased the risk of Type 2 diabetes.[34] Additional biomedical and biochemical studies including subjects with protective protein dysfunctions should be immediately conducted.

In conclusion, the activities of protective proteins in the circulation significantly decrease and deform in the presence of low level of systemic inflammation, excessive oxidative process, hypertriglyceridemia, dyslipidemia, and MetS, suggesting an equal to or greater effect on CHD in Turkish adults as conventional risk factors.

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