What a low prevalence of diabetes mellitus between the most desired values of high density lipoproteins in the plasma

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Abstract

Background: We tried to understand the most desired values of high density lipoproteins (HDL) in the metabolic syndrome.

Methods: Patients with plasma HDL values lower than 40 mg/dL were collected into the first, lower than 46 mg/dL into the second, lower than 50 mg/dL into the third, and 50 mg/dL and higher into the fourth groups.

Results: The study included 256 cases (153 females). Parallel to the highest HDL values, mean age, female ratio, body mass index (BMI), fasting plasma glucose (FPG), low density lipoproteins (LDL), white coat hypertension (WCH), hypertension (HT), and diabetes mellitus (DM) were the highest in the fourth group. Whereas coronary heart disease (CHD) was the highest in the first group in contrast to the lowest HDL and LDL values. Interestingly, BMI, FPG, WCH, DM, and CHD were the lowest in the second group, and prevalence of DM was only 3.1% in this group against 22.2% of the others ($p<0.001$).

Conclusions: The highest mean age, female ratio, BMI, FPG, WCH, HT, and DM parallel to the highest HDL and LDL, and the highest CHD in contrast to the lowest HDL and LDL values may show initially positive but eventually negative acute phase proteins features of HDL and LDL. BMI, FPG, DM, and CHD were the lowest between HDL values of 40 and 46 mg/dL, and DM was only 3.1% between these values against 22.2% of the remaining. The moderate HDL values may also be a result, instead of a cause of the lower prevalence of DM.

Key words: High density lipoproteins, diabetes mellitus, low density lipoproteins, triglycerides, acute phase proteins, body mass index, metabolic syndrome

Introduction

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of end-organ insufficiencies, aging, and death in the human being (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying mechanism by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term venosclerosis is not famous in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, and eventually reduce blood flow to terminal organs and increase systolic BP further. Some of the well-known underlying causes and indicators of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), chronic inflammations and infections, and prolonged cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, early aging, and premature death (5-10). Although early withdrawal of the underlying causes can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The underlying causes and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (11-13). Although their normal limits have not been determined clearly yet, increased plasma triglycerides values may be one of the most sensitive indicators of the metabolic syndrome (14-17). Due to the growing evidence about the strong association between higher plasma triglycerides and prevalence of CHD, Adult Treatment Panel (ATP) III determined lower cutpoints for triglycerides abnormalities than did ATP II (18, 19). Although ATP II determined the normal plasma triglycerides values as lower than 200 mg/dL in 1994 (19), World Health Organisation in 1999 (20) and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL (18). Although these cutpoints, there are still suspicions about the safest values of plasma triglycerides in the plasma (15-17). Beside that although the higher sensitivity of plasma triglycerides in the metabolic syndrome, basic functions and desired values of high density lipoproteins (HDL) and low density lipoproteins (LDL) are still suspicious (21). We tried to understand the most desired values of HDL in the metabolic syndrome.

Material and Methods

The study was done in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at the age of 15 years and greater were included into the study. Medical pasts of the cases including HT, DM, COPD, and already used medications were learned, and a routine check up including fasting plasma glucose (FPG), HDL, LDL, and triglycerides was performed. Current daily smokers with six pack-months and cases with a past of three pack-years were accepted as smokers. Due to the very low prevalence of alcoholism in Turkey (22), we did not include regular alcohol intake into the study. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on body weight. Additionally, anti-hyperlipidemic drugs, metformin, and acarbose users were excluded to avoid their possible effects on blood lipid profiles and body weight (23, 24). Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (18). Patients with an overnight FPG value of 126 mg/dL and higher on two occasions or already using antidiabetic medications were defined as diabetics (18). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG value between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose value of 200 mg/dL and greater is DM (18). Additionally, office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in the normotensives in the office due to the risk of masked HT after a 10-minutes of education about proper BP measurement techniques (25). An additional 24-hour ambulatory blood pressure monitoring was not taken due to the similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 140/90 mmHg and higher on HBP measurements, and WCH as an OBP of 140/90 mmHg and higher but a mean HBP measurement of lower than 140/90 mmHg (25). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as the already developed movement disorders in the cardiac walls. The spirometric pulmonary function tests were performed in required cases after the physical examination, and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (26). Finally, patients with plasma HDL values lower than 40 mg/dL were collected into the first, lower than 46 mg/dL into the second, lower than 50 mg/dL into the third, and 50 mg/dL and higher into the fourth groups, respectively. The mean age, female ratio, smoking, BMI,

FPG, triglycerides, LDL, HDL, WCH, HT, DM, COPD, and CHD were detected in each group, and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 256 cases (153 females and 103 males), totally. Parallel to the highest HDL values, the mean age, female ratio, BMI, FPG, LDL, WCH, HT, and DM were the highest in the fourth group. Whereas CHD was the highest in the first group in contrast to the lowest HDL and LDL values. Interestingly, the mean age, female ratio, BMI, FPG, WCH, DM, and CHD were the lowest in the second group. But the difference was the greatest for DM, and its prevalence was only 3.1% in the second group against 21.3% (p<0.001) of the first, 22.2% (p<0.001) of the third, and 23.2% (p<0.001) of the fourth groups. Triglycerides were also the highest parallel to the highest prevalence of smoking in the second group, and they were the lowest parallel to the lowest prevalence of smoking in the fourth group. So prevalence of smoking was parallel with the male ratio in the study (Table 1).

Table 1: Characteristics features of the cases according to high density lipoproteins values in the plasma

Variable	Lower than 40 mg/dL	*p*-value	Lower than 46 mg/dL	*p*-value	Lower than 50 mg/dL	*p*-value	50 mg/dL and higher
Number	75		63		45		73
Age (year)	45.4 ± 15.2 (16-79)	Ns*	45.3 ± 15.1 (19-78)	Ns	*46.5 ± 13.5 (19-73)*	*0.026*	*51.8 ± 11.6 (21-77)*
Female ratio	46.6%	Ns	*42.8%*	*0.001>*	*66.6%*	*0.01>*	*83.5%*
Smoking	34.6%	Ns	36.5%		24.4%	Ns	17.8%
BMI† (kg/m^2)	27.2 ± 4.5 (18.4-39.9)	Ns	*25.7 ± 4.2 (18.6-34.3)*	*0.024*	*27.7 ± 4.6 (19.6-36.0)*	Ns	29.3 ± 6.1 (17.8-48.6)
FPG‡ (mg/dL)	*119.4 ± 48.4 (76-287)*	*0.006*	*97.6 ± 13.5 (67-154)*	Ns	114.9 ± 59.0 (63-386)	Ns	134.1 ± 77.0 (74-400)
Triglycerides (mg/dL)	162.7 ± 92.8 (43-470)	Ns	175.3 ± 103.0 (27-617)	Ns	144.9 ± 72.2 (47-411)	Ns	134.5 ± 81.5 (37-418)
LDL§ (mg/dL)	*105.3 ± 33.1 (10-211)*	*0.000*	*126.0 ± 32.7 (39-197)*	Ns	134.7 ± 36.6 (77-223)	Ns	135.3 ± 32.3 (54-239)
HDL‖ (mg/dL)	*34.1 ± 3.8 (22-39)*	*0.000*	*42.8 ± 1.6 (40-45)*	*0.000*	*47.5 ± 1.1 (46-49)*	*0.000*	*58.2 ± 8.0 (50-91)*
WCH**	25.3%	Ns	23.8%	Ns	31.1%	Ns	36.9%
HT***	10.6%	Ns	11.1%	Ns	*17.7%*	*0.05>*	*28.7%*
DM****	*21.3%*	*0.001>*	*3.1%*	*0.001>*	*22.2%*	Ns	23.2%
COPD*****	14.6%	Ns	17.4%	Ns	20.0%	Ns	10.9%
CHD******	*20.0%*	*0.05>*	*11.1%*	Ns	13.3%	Ns	16.4%

***Nonsignificant (p>0.05) †Body mass index ‡Fasting plasma glucose §Low density lipoproteins ‖High density lipoproteins **White coat hypertension ***Hypertension ****Diabetes mellitus *****Chronic obstructive pulmonary disease ******Coronary heart disease**

Discussion

Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma (27, 28). Excess weight-induced chronic low-grade vascular endothelial inflammation plays a significant role in the pathogenesis of accelerated atherosclerosis in the whole body (1, 2). Additionally, excess weight leads to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors eventually terminate with increased risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI in the other studies (29, 30), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (31). The relationship between excess weight, elevated BP, and hypertriglyceridemia is described in the metabolic syndrome (14), and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (12). For example, prevalence of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in a previous study (32). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia and control groups in the same study (32). Additionally, although the higher plasma trigycerides values, LDL values were also lower in the group with the plasma HDL levels lower than 40 mg/dL in the other study ($p<0.001$ for all) (33). Similarly, plasma triglycerides were higher in the first group with the lowest LDL and HDL values in the present study. On the other hand, the lowest triglycerides value of the fourth group can be explained by the lowest prevalencesof smoking and male ratio since there is a significant relationship between hypertriglyceridemia, smoking, and male ratio (34, 35).

Probably, alcohol and smoking are also found among the most common causes of vasculitis. Both of them cause a chronic inflammatory process on the vascular endothelium depending on the concentrations of products of alcohol and smoke in the blood. So both of them can cause an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Thus both of them should be added into the major components of the metabolic syndrome. Atherosclerotic effects of smoking are the most obvious in Buerger's disease. It is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. On the other hand, smoking in the human being and nicotine administration in animals may be associated with decreased BMI values (36). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (37). According to an animal study, nicotine lengthens intermeal time and decreases amount of meal eaten (38). Additionally, the mean BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (39). Smoking may be associated with a postcessation weight gain (40). Similarly, although CHD was detected with similar prevalence in both genders, prevalence of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (41). Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (42). In another definition, smoking may be more dangerous for women due to the associated weight excess and its consequences. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite (43). Smoking-induced weight loss may be related with the smoking-induced chronic vascular endothelial inflammation all over the body since loss of appetite is one of the major symptoms of the disseminated inflammation in the body. Physicians can even understand healing of the patients by means of normalizing appetite of them. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a vascular endothelial inflammation until clearance from the circulation. But due to the repeated smoking habit, the clearance never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (37-39). After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weight is the patients' physiological weight, actually.

Although ATP III reduced the normal limits of plasma triglycerides as lower than 150 mg/dL in 2001 (18), much lower values may indicate better health conditions (15-17). For example, the greatest number of clinical and laboratory deteriorations was observed just above the plasma triglycerides value of 60 mg/dL in the above study (17). Similar to the present study, prevalence of smoking was the highest with the highest triglycerides values in the other study (16) that may also indicate the inflammatory role of smoking in the metabolic syndrome, since triglycerides may actually be sensitive acute phase reactants in the plasma. In the above study (16), the mean age, male ratio, smoking, BMI, FPG, WCH, HT, DM, and COPD increased parallel to the increased plasma triglycerides values from the first up to the fifth groups, gradually. On the other hand, increased plasma triglycerides values by aging may be secondary to the aging-induced decreased physical and mental stresses, those eventually terminate with onset of excess weight and its consequences. Although the borderline high triglycerides values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high (200-499 mg/dL) and very high triglycerides values (500 mg/dL and greater) may be secondary to smoking, genetic factors, and terminal consequences of the metabolic syndrome such as obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (18). But although the underlying causes of the borderline high, high, and very high plasma triglycerides values may be a little bit different, probably risks of the terminal consequences do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the group with the highest triglycerides values in the above study (16). Eventually, although some authors reported that lipid assessment can be simplified

as the measurements of total cholesterol and HDL values alone (44), the present study and most others indicated significant relationships between plasma triglycerides, HDL, and LDL values and terminal consequences of the metabolic syndrome (33, 45).

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of the animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. Triglycerides are the major lipids of the fat tissue. Phospholipids are triglycerides that are covalently bound to a phosphate group, and regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, triglycerides, and phospholipids do not circulate freely in the plasma, instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins in the plasma. Chylomicrons carry exogenous triglycerides to the liver via the thoracic duct. Very low density lipoproteins (VLDL) are produced in liver, and carry endogenous triglycerides to the peripheral organs. In the capillaries of adipocytes and muscle tissue, VLDL are converted into intermediate density lipoproteins (IDL) by removal of 90% of triglycerides by lipases. Then IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL deliver cholesterol from the liver to the peripheral organs. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors of the macrophages that migrate into the arterial walls, and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells including the arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs such as adrenals, ovaries, and testes for excretion, re-utilization, and disposal. All of the carrier lipoproteins are under dynamic control, and are readily affected by diet, illness, drug, and weight excess. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is a low grade inflammatory process on vascular endothelium. Thus the metabolic syndrome alone may be a cause of abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called 'the good cholesterol' due to their role in removing excess cholesterol from the blood and protecting the arterial wall against atherosclerosis (46), recent studies did not show similar results, and low plasma HDL values may alert us to searching for some inflammatory pathologies in the body (47-49). Normally, HDL show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (47). However, HDL may become 'dysfunctional' in pathological conditions which means that relative composition of lipids and proteins, as well as the enzymatic activities of HDL are altered (47). For example, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation of HDL, as well as the transformation of HDL proteomes into the proinflammatory proteins. Additionally, three highly effective agents for increasing HDL levels including niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, and stroke (50). In other words, while higher HDL values may correlate with better cardiovascular health, specifically increasing one's HDL may not increase cardiovascular health (50). So they may just be some indicators instead of the main actors in the metabolic syndrome. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD (51). For example, although the similar mean age, gender distribution, smoking, and BMI in both groups, DM and CHD were higher in the group with the plasma HDL values lower than 40 mg/dL in the above study (33). Similarly, although the lower mean age, BMI, FPG, LDL, and HDL, the highest CHD of the first group may also indicate eventual features of HDL as the negative acute phase proteins (APP) in the present study.

APP are a group of proteins whose plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damage (52-54). In case of inflammation, infection, and tissue damage, neutrophils and macrophages release cytokines into the blood. The liver responds by producing many positive APP to them. At the same time, production of some proteins are reduced. Thus these proteins are called negative APP. Some of the well-known negative APP are albumin, transferrin, retinol-binding protein, antithrombin, and transcortin. The decrease of such proteins is also used as an indicator of inflammation. The physiological role of decreased synthesis of such proteins may be protection of amino acids for production of positive APP, effectively. Due to the same reason, production of HDL and LDL may also be suppressed in the liver. By this way, although the similar mean age, gender distribution, smoking, and BMI in both groups, the higher triglycerides, DM, and CHD against the significantly lower HDL and LDL values can be explained in the above study (33). Beside that although the lower mean age, BMI, FPG, LDL, and HDL, the highest CHD of the first group can also be explained by the same theory in the present study. Similarly, although the mean triglycerides, fibrinogen, C-reactive protein, and glucose values were higher in cases with ischemic stroke, the oxidized LDL values did not correlate with age, stroke severity, and outcome in another study (55). Additionally, significant alterations occurred in the lipid metabolism and lipoproteins composition during infections, and triglycerides increased whereas HDL and LDL decreased in another study (56). Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study (57). Similarly, the highest HT and DM parallel to the increased LDL and HDL values, and the highest COPD, CHD, and CRD in contrast to the lowest LDL and HDL values may show initially positive but eventually negative acute phase proteins functions of LDL and HDL in the metabolic syndrome in another study (58), and the safest values of LDL were between 80 and 100 mg/dL in the plasma in the same study (58).

There may be several mechanisms of the significantly lower prevalence of DM between the HDL values of 40 and 46 mg/dL in the present study. According to the results of our previous studies, the moderate HDL values may not

be a cause, instead just be a result of the lower prevalence of DM between these HDL values in the plasma. Since chronic hyperglycemia may cause a chronic low grade inflammation on vascular endothelium all over the body, and the inflammation may initially increase but eventually decrease HDL production by the liver. Secondly, DM may cause a relative immunosuppression increasing risks of various infections all over the body. In this way, HDL production of the liver can be altered again. Thirdly, chronic hyperglycemia alone may cause a relative hepatic dysfunction and decrease production of HDL by the liver. Even diabetic nephropathy induced proteinuria may decrease HDL production of the liver. In another definition, there may be hundreds of mechanisms with variable priorities for the significantly lower prevalence of DM between the HDL values of 40 and 46 mg/dL in the plasma, and the result of the study should not be surprising for us.

As a conclusion, the highest mean age, female ratio, BMI, FPG, WCH, HT, and DM parallel to the highest HDL and LDL, and the highest CHD in contrast to the lowest HDL and LDL values may show initially positive but eventually negative acute phase proteins features of HDL and LDL. BMI, FPG, DM, and CHD were the lowest between HDL values of 40 and 46 mg/dL, and the prevalence DM was only 3.1% between these values against 22.2% of the others. The moderate HDL values may also be a result instead of a cause of the lower prevalence of DM.

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