HIGH AND LOW DENSITY LIPOPROTEINS MAY BE NEGATIVE ACUTE PHASE PROTEINS OF THE METABOLIC SYNDROME

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Abstract

Background: We tried to understand whether or not high density lipoproteins (HDL) and low density lipoproteins (LDL) may be negative acute phase proteins (APP) of the metabolic syndrome.
Methods: Patients with plasma HDL values lower than 40 mg/dL were collected into the first group, and then age and gender matched patients with plasma HDL values 40 mg/dL and greater were collected into the second group, and compared in between.

Results: There were 75 patients in the first and 118 patients in the second groups. Smoking (34.6 versus 31.3%), body mass index (BMI) (27.2 versus 26.7 kg/m2), fasting plasma glucose (119.4 versus 113.0 mg/dL), white coat hypertension (25.3 versus 32.2%), hypertension (10.6 versus 16.1%), and chronic obstructive pulmonary disease (14.6 versus 18.6%) were similar in both groups ($p>0.05$ for all). Although triglycerides (162.7 versus 125.4 mg/dL, $p<0.001$), diabetes mellitus (DM) (21.3 versus 12.7%, $p<0.05$), and coronary heart disease (CHD) (20.0 versus 11.0%, $p<0.05$) were higher, LDL (105.3 versus 126.2 mg/dL, $p<0.000$) and HDL (34.1 versus 50.0 mg/dL, $p<0.000$) were lower in patients with plasma HDL values lower than 40 mg/dL.

Conclusions: Although the similar mean age, gender distribution, smoking, and BMI in both groups, triglycerides, DM, and CHD were higher whereas LDL and HDL were lower in patients with plasma HDL values lower than 40 mg/dL. So HDL and LDL may be negative APP of the metabolic syndrome.

Key words: High density lipoproteins, low density lipoproteins, triglycerides, acute phase proteins, metabolic syndrome

Introduction

Chronic endothelial damage may be the most common kind of vasculitis, and the leading cause of early aging and premature 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 predominantly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature that reduces blood flow to terminal organs, and increases systolic BP further. Some of the well-known components of the inflammatory process are physical inactivity, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), rheumatologic disorders, chronic infections, and cancers for the development of terminal endpoints 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, early aging, and premature death (5-10). Although early withdrawal of the predisposing factors may delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. Up to now, the predisposing factors and terminal endpoints were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medicine, extensively (11-14). Although its normal limits have not been determined clearly yet, increased plasma triglycerides may be one of the most sensitive parameters of the metabolic syndrome (15-18). Due to the growing evidence about the strong association between higher plasma triglycerides values and prevalence of CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (19, 20). Although ATP II determined the normal plasma triglycerides value as lower than 200 mg/dL in 1994 (20), World Health Organisation in 1999 (21) and ATP III in 2001 reduced their normal limit as lower than 150 mg/dL (19). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are still suspicions about the safest value of plasma triglycerides in the medical literature (16-18). Although the absolute sensitivity of plasma triglycerides in the metabolic syndrome, roles of high density lipoproteins (HDL) and low density lipoproteins (LDL) are suspicious (22). We tried to understand whether or not HDL and LDL may be negative acute phase proteins (APP) of the metabolic syndrome

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at and above the age of 15 years were included. Their medical histories including HT, DM, COPD, and already used medications were learned, and a routine check up procedure including fasting plasma glucose (FPG), HDL, LDL, and triglycerides was performed. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. Due to the very low prevalence of alcoholism in Turkey (23), 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 weight. Additionally, anti-hyperlipidemic drugs, metformin, and/or acarbose users were excluded to avoid their possible effects on blood lipid profiles and/or body weight (24, 25). 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 (19). Cases with an overnight FPG value of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (19). 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 or greater is DM (19). 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 minute education session about proper BP measurement techniques (26). An additional 24-hour ambulatory blood pressure monitoring was not needed due to its similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 135/85 mmHg or greater on HBP measurements, and WCH as an OBP of 140/90 mmHg or greater but a mean HBP measurement of lower than 135/85 mmHg (26). 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 due to 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% (27). Eventually, patients with plasma HDL values lower than 40 mg/dL were collected into the first group, and then age and gender matched patients with plasma HDL values 40 mg/dL and greater were collected into the second group, respectively. 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

There were 75 patients in the first and 118 patients in the second groups. The mean age (45.4 versus 47.9 years) and male ratio (53.3 versus 53.3%) were similar in both groups (p>0.05 for both). Smoking (34.6 versus 31.3%), BMI (27.2 versus 26.7 kg/m2), FPG (119.4 versus 113.0 mg/dL), WCH (25.3 versus 32.2%), HT (10.6 versus 16.1%), and COPD (14.6 versus 18.6%) were similar in both groups, too (p>0.05 for all). Although the mean triglycerides (162.7 versus 125.4 mg/dL, p<0.001), DM (21.3 versus 12.7%, p<0.05), and CHD (20.0 versus 11.0%, p<0.05) were higher, LDL (105.3 versus 126.2 mg/dL, p<0.001) and HDL (34.1 versus 50.0 mg/dL, p<0.001) were lower in patients with plasma HDL values lower than 40 mg/dL, significantly (Table 1).

Table 1: Characteristic features of the study cases according to the plasma high density lipoproteins values

Variable	Lower than 40 mg/dL	*p*-value	40 mg/dL and higher
Number of cases	75		118
Mean age (year)	45.4 ±15.2 (16-79)	Ns*	47.9 ±14.6 (19-77)
Male ratio	53.3%	Ns	53.3%
Smoking	34.6%	Ns	31.3%
BMI† (kg/m^2)	27.2 ±4.5 (18.4-39.9)	Ns	26.7 ±5.0 (17.8-42.4)
FPG‡ (mg/dL)	119.4 ±48.4 (76-287)	Ns	113.0 ±54.2 (63-400)
Triglycerides (mg/dL)	*162.7 ± 92.8 (43-470)*	*<0.001*	*125.4 ± 73.2 (27-410)*
LDL§ (mg/dL)	*105.3 ± 33.1 (10-211)*	*<0.000*	*126.2 ± 29.5 (54-202)*
HDL‖ (mg/dL)	*34.1 ± 3.8 (22-39)*	*<0.000*	*50.0 ± 9.1 (40-91)*
WCH**	25.3%	Ns	32.2%
HT***	10.6%	Ns	16.1%
*DM****	*21.3%*	*<0.05*	*12.7%*
COPD*****	14.6%	Ns	18.6%
*CHD******	*20.0%*	*<0.05*	*11.0%*

*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

Excess weight may lead to both structural and functional abnormalities of many organs of the body. Adipose tissues produce leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma (28, 29). Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerosis in the whole body (1, 2). Additionally, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors will eventually terminate with increased left ventricular stroke work and risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI values in the other studies (30, 31), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (32). The relationship between excess weight, elevated BP, and plasma triglycerides is described in the metabolic syndrome (15), and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (13). Similarly, prevalence of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in the other study (33). On the other hand, the prevalence of increased LDL cases were similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (33). Similarly, although the significantly higher trigycerides ($p<0.001$), plasma LDL and HDL values were lower in cases with plasma HDL levels lower than 40 mg/dL in the present study ($p<0.000$ for both).

Smoking may be found among one of the most common causes of vasculitis all over the world. It causes a chronic inflammatory process on the vascular endothelium, probably depending on the concentration of smoke that terminates with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Therefore smoking has to be included among the major components of the metabolic syndrome. Strong and terminal atherosclerotic effects of smoking are the most obviously seen in the Buerger's disease (thromboangiitis obliterans). 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 medical literature. Although the well-known strong atherosclerotic effects of smoking, smoking in the human being and nicotine administration in animals may be associated with decreased BMI values (34). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (35), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (36). According to an animal study, nicotine may lengthen intermeal time and decrease amount of meal eaten (37). Additionally, the mean BMI seems to be the highest in the former, the lowest in the current and medium in never smokers (38). Smoking may be associated with a postcessation weight gain (39). Similarly, although CHD was detected with similar prevalences in both genders, prevalence of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (40). Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (41). In another definition, smoking may be more dangerous for women probably due to the associated higher BMI and its consequences in them. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (25). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite (42). 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 inflammations in the body. Physicians can even understand healing of the patients via their normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a vascular endothelial inflammation until their clearance from the circulation. But due to the repeated smoking habit of the individuals, the clearance process 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 (36-38). After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weights are the patients' physiological weights, actually.

Although ATP III reduced the normal limit of plasma triglycerides as lower than 150 mg/dL in 2001 (19), much lower limits may provide additional benefit for health (16-18). In the above study (17), prevalence of smoking was the highest in the highest triglycerides having group which may also indicate inflammatory roles of smoking in the metabolic syndrome, since triglycerides may actually be some acute phase reactants in the metabolic syndrome. The mean age, male ratio, smoking, BMI, FPG, WCH, HT, DM, and COPD increased parallel to the plasma triglycerides values from the first towards the fifth groups, continuously (17). In our opinion , significantly increased plasma triglycerides values by aging may be secondary to aging-induced decreased physical and mental stresses, those eventually terminate with onset of excess weight and many associated health problems. Although the borderline high triglycerides values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL or greater) may be secondary to both genetic factors and terminal consequences of the metabolic syndrome including

smoking, obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (19). But although the underlying causes of the high and very high plasma triglycerides values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the highest triglycerides having group in the above study (17). Eventually, although some authors reported that lipid assessment can be simplified as the measurements of total cholesterol and HDL values alone (43), the present study and most of the others indicated significant relationships between plasma triglycerides, HDL, and LDL values and terminal consequences of the metabolic syndrome (44).

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. Triglycerides are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of our body's fat tissue is in the form of triglycerides. Phospholipids are triglycerides that are covalently bound to a phosphate group. Phospholipids 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 including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL. Chylomicrons carry exogenous triglycerides from intestine to liver via the thorasic duct. VLDL are produced in liver, and carry endogenous triglycerides from the liver to the peripheral organs including adipocytes and muscle tissue. In the capillaries of adipocytes and muscle tissue, 90% of triglycerides is removed by a specific group of lipases. So VLDL are converted into IDL by removal of triglycerides. Then IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma. LDL deliver cholesterol from the liver to the parts of body. Although the liver removes majority of LDL from the circulation, a small amount is uptaken by scavenger receptors on macrophages that may migrate into arterial walls, where they become the foam cells of atherosclerotic plaques. HDL removes fats and cholesterol from cells, including within artery 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 in the plasma are under dynamic metabolic control, and are readily affected by diet, illnesses, drugs, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is an abnormal condition with a low grade inflammatory process on vascular endothelium all over the body. 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 as 'the good cholesterol' due to their roles in removing excess cholesterol from the blood and protecting the arterial walls against atherosclerosis (45), recent studies did not show similar results, and low plasma HDL levels may alert searching of additional metabolic and inflammatory pathologies in the body (46-48). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory features (46). 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 (46). For instance, 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 proinflammatory proteins. Additionally, neither niacin, fibrates, nor cholesteryl ester transfer protein inhibitors, three highly effective agents about increasing HDL levels, reduced all cause mortality, CHD mortality, myocardial infarction, or stroke in patients treated with statins (49). While higher HDL levels are correlated with cardiovascular health, no medication used to increase HDL has been proven to improve health (49). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL may not increase cardiovascular health (49). So they may actually be just indicators instead of the main actors of the process. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased, rather than decreased, risk for CHD (50). Similarly, although the similar mean age, gender distribution, smoking, and BMI in both groups, DM and CHD were significantly higher in patients with plasma HDL values lower than 40 mg/dL in the present study.

APP are a class of proteins whose plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damage (51-53). In case of inflammation, infection, and tissue damage, local inflammatory cells (neutrophils and macrophages) secrete several kinds of cytokines into the blood, most notable of which are the interleukins. The liver responds by producing many positive APP. At the same time, productions of many proteins are reduced. Therefore these proteins are called as 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 is generally to save amino acids for producing positive APP, effectively. Due to the decreased production of some proteins in liver during severe inflammatory conditions, production of HDL and LDL may also be suppressed. By this way, although the similar mean age, gender distribution, smoking, and BMI in both groups, the higher triglycerides, DM, and CHD against the lower HDL and LDL values in patients with plasma HDL values lower than 40 mg/dL can be explained in the present study. Similarly, although the mean triglycerides, fibrinogen, C-reactive protein, and glucose values were significantly higher in cases with

ischemic stroke, the oxidized LDL values did not correlate with age, stroke severity, and outcome in the other study (54). Additionally, significant alterations occurred in lipid metabolism and lipoprotein composition during infections, and triglycerides increased whereas HDL and LDL decreased in another study (55). Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study (56).

As a conclusion, although the similar mean age, gender distribution, smoking, and BMI in both groups, triglycerides, DM, and CHD were higher whereas LDL and HDL were lower in patients with plasma HDL values lower than 40 mg/dL, significantly, so HDL and LDL may be negative APP of the metabolic syndrome.

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