High density lipoproteins may act in a similar direction with low density lipoproteins in the metabolic syndrome

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ABSTRACT

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

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

Results: There were 183 patients in the first and 73 patients in the second groups. Although the male ratio (49.7 versus 16.4%, p<0.001), smoking (32.7 versus 17.8%, p<0.01), plasma triglycerides values (162.7 versus 134.5 mg/dL, p= 0.005), and chronic obstructive pulmonary disease (COPD) (16.9 versus 10.9%, p<0.05) decreased, the mean age (45.6 versus 51.8 years, p= 0.002), body mass index (BMI) (26.8 versus 29.3 kg/m2, p= 0.013), fasting plasma glucose (FPG) (110.8 versus 134.1 mg/dL, p= 0.02), low density lipoproteins (LDL) (119.6 versus 135.3 mg/dL, p<0.001), white coat hypertension (WCH) (26.2 versus 36.9%, p<0.05), hypertension (HT) (13.6 versus 28.7%, p<0.001), and diabetes mellitus (DM) (15.3 versus 23.2%, p<0.05) increased by the increased plasma HDL values (40.4 versus 58.2 mg/dL, p<0.000), significantly. Whereas coronary heart disease did not change, probably due to the effects of smoking on the first, and aging and excess weight on the second groups.

Conclusions: Though the decreased male ratio, smoking, plasma triglycerides values, and COPD, the mean age, BMI, FPG, LDL, WCH, HT, and DM increased by the increased plasma HDL values, HDL may act in a similar direction with LDL in the metabolic syndrome.

Key words: High density lipoproteins, low density lipoproteins, triglycerides, male gender, smoking, excess weight, accelerated atherosclerosis, metabolic syndrome

Introduction

Chronic low-grade endothelial inflammation may be the most common type of vasculitis, and the leading cause of aging in human beings (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by triggering recurrent injuries on endothelium. Probably whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic low-grade endothelial injury, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, all of which reduces blood supply to the end-organs, and increases systolic BP further. Some of the well-known underlying causes and/or indicators of the inflammatory process are physical inactivity, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), cancers, prolonged infections such as tuberculosis, and chronic inflammations such as rheumatologic disorders (5, 6). Some of the irreversible consequences of the chronic low-grade inflammatory process include obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, early aging, and premature death (7-9). Although early withdrawal of the underlying causes may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, stroke, or early aging, endothelial destruction cannot be reversed effectively due to their fibrotic nature. The triggering etiologies and terminal consequences of the chronic low-grade inflammatory process are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (10-13). Although the absolute significance of plasma triglycerides in the metabolic syndrome, role of high density lipoproteins (HDL) is suspicious (19). We tried to understand the prognostic significance of HDL in the metabolic syndrome in the present study. Due to the significant association between high plasma triglycerides and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (15, 16). Although ATP II determined the normal upper limit of triglycerides as 200 mg/dL in 1994, World Health Organisation in 1999 (17) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (16). Despite these cutpoints, there are several reports about the lower and safer limits of the triglycerides in the literature (18-20). Tthough the absolute significance of plasma triglycerides in the metabolic syndrome, role of high density lipoproteins (HDL) is suspicious (19). We tried to understand the prognostic significance of HDL in the metabolic syndrome in the present study.

Materials and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients above the age of 15 years were studied. Their medical histories were learnt, and a routine check up procedure including fasting plasma glucose (FPG), serum creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, triglycerides, low density lipoproteins (LDL), HDL, an electrocardiogram, and an abdominal ultrasonography was performed. A Doppler echocardiogram was performed just in required cases. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. Patients with devastating illnesses including type 1 DM, malignancies, hemodialysis, ascites, 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 (21, 22). 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 (16). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (16). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM (16). 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 -hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases after a 10-minute education about proper BP measurement techniques (23). An additional 24-hour ambulatory blood pressure monitoring was not required due to its similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 135/85 mmHg or higher on HBP measurements, and WCH as an OBP of 140/90 mmHg or higher but a mean HBP measurement of lower than 135/85 mmHg (23). 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 and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (24). Eventually, patients with plasma HDL values lower than 50 mg/dL were put into the first and 50 mg/dL and higher into the second groups, respectively. The mean age, male 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

There were 183 patients in the first and 73 patients in the second groups. Although the male ratio (49.7 versus 16.4%, p<0.001), smoking (32.7 versus 17.8%, p<0.01), plasma triglycerides values (162.7 versus 134.5 mg/dL, p= 0.005), and COPD (16.9 versus 10.9%, p<0.05) decreased, the mean age (45.6 versus 51.8 years, p= 0.002), BMI (26.8 versus 29.3 kg/m2, p= 0.013), FPG (110.8 versus 134.1 mg/dL, p= 0.02), LDL (119.6 versus 135.3 mg/dL, p<0.001), WCH (26.2 versus 36.9%, p<0.05), HT (13.6 versus 28.7%, p<0.001), and DM (15.3 versus 23.2%, p<0.05) increased by the increased plasma HDL values (40.4 versus 58.2 mg/dL, p<0.000), significantly. On the other hand, CHD did not change between the study groups probably due to the effects of smoking on the first and excess weight and aging on the second groups (Table 1).

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

Variable	Lower than 50 mg/dL	*p*-value	50 mg/dL and higher
Number of cases	183		73
Mean age (year)	*45.6 ± 14.7 (16-79)*	*0.002*	*51.8 ± 11.6 (21-77)*
Male ratio	*49.7%*	*<0.001*	*16.4%*
Smoking	*32.7%*	*<0.01*	*17.8%*
BMI (kg/m²)*	*26.8 ± 4.5 (18.4-39.9)*	*0.013*	*29.3 ± 6.1 (17.8-48.6)*
FPG† (mg/dL)	*110.8 ± 44.2 (63-386)*	*0.02*	*134.1 ± 77.0 (74-400)*
Triglycerides (mg/dL)	*162.7 ± 92.3 (27-617)*	*0.005*	*134.5 ± 81.5 (37-418)*
LDL‡ (mg/dL)	*119.6 ± 35.8 (10-223)*	*<0.001*	*135.3 ± 32.3 (54-239)*
HDL§ (mg/dL)	*40.4 ± 6.1 (22-49)*	*<0.000*	*58.2 ± 8.0 (50-91)*
WCH?	*26.2%*	*<0.05*	*36.9%*
*HT***	*13.6%*	*<0.001*	*28.7%*
*DM****	*15.3%*	*<0.05*	*23.2%*
*COPD*****	*16.9%*	*<0.05*	*10.9%*
CHD*****	15.3%	Ns******	16.4%

*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

******Nonsignificant (p>0.05)

Discussion

Excess weight may be the most common cause of vasculitis worldwide, and the leading cause of major health problems in this century, since nearly three-quarters of cases above the age of 30 years have excess weight, nowadays (25). Excess weight causes a chronic low-grade vascular endothelial inflammation, terminating with an accelerated atherosclerotic process all over the body (26). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines; all of those behave as acute phase reactants in the plasma (27). Beside that, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of an 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. Additionally, FPG and total cholesterol (TC) increased, parallel to the increased BMI values (28). A combination of these cardiovascular risk factors will eventually terminate with an increase in left ventricular stroke work and higher 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 study (29), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (30). The relationships between excess weight, increased BP, and higher plasma triglycerides values are well-known in the metabolic syndrome (14). 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 (31). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia (200 mg/dL and greater) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) (31). Similarly, plasma LDL values increased just up to the plasma triglycerides value of 200 mg/dL in the above study (20). Beside that, the mean BMI values increased just up to the plasma triglycerides value of 150 mg/dL, significantly ($p<0.05$ for each step) (20). In our opinion, although excess weight does not affect each individual with the same severity, overweight, obesity, severe obesity, and morbid obesity histories of years should be added into the calendar age with various degrees during calculation of physiological age of the individuals.

Smoking and alcohol may be the second and third most common causes of vasculitis, respectively. According to our experience, both of them should be included into the major components of the metabolic syndrome since they cause chronic inflammation on the vascular endothelium, terminating with an accelerated atherosclerotic process all over the body. Tobacco's destructive effects are particularly prominent in the respiratory tract and lungs, probably due to the highest concentrations of toxic substances found in the cigarette smoke there. The strong and irreversible atherosclerotic effects of tobacco are most clearly detected 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. Eventually, the atherosclerotic effects terminate with early aging, end-organ insufficiencies, and premature death (32). According to our clinical observations, although tobacco does not affect each individual with the same severity, the smoking history of pack-years should be added into the calendar age during calculation of physiological age of the patients. Probably, alcohol gives harm to vascular endothelium by means of similar ways with smoking but alcohol's main targets are the gastrointestinal tract and liver due to the highest concentrations of alcohol and its products there. Thus the drinking history of drink-years should also be added into the calendar age during calculation of physiological age of the individuals. Due to the very low prevalence of alcoholism in Turkey (33), we did not include regular alcohol intake into the present study. On the other hand, although alcoholic drinks provide extra calories for body, smoking in humans and nicotine administration in animals may be associated with a decreased BMI (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 simultaneously decrease amount of meal eaten (37). Additionally, BMI seems to be the highest in former and lowest in current smokers (38). Smoking may be associated with a postcessation weight gain (39). 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 in the previous study (40). Additionally, the incidence of 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 higher BMI and its consequences in them. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite (42). Smoking-induced appetite loss may be related with the smoking-induced vascular endothelial inflammation in whole body, since loss of appetite is one of the major symptoms of disseminated inflammation in the body. Physicians can even understand healing of patients by means of their normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract and lungs, and cause a vascular endothelial inflammation in whole body until their clearance from the circulation. But due to the repeated smoking habit of the individuals, 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 (36-38). After smoking cessation, appetite normalizes with a prominent weight gain but the returned weight is the patients' physiological weight, actually.

The prevalence of excess weight increased by decades, particularly after the third decade, up to the eight decade of life (25). So 30th and 70th years of age may be the breaking points of life for body weight, and aging may be the major determiner factor of excess weight. Probably, partially decreased physical and mental stresses after the age of 30 years, and debility and comorbid disorders-induced restrictions after the age of 70 years may be the major causes of the changes of BMI at these ages. Interestingly, the mean age and BMI increased just up to the plasma triglycerides values of 200 mg/dL and 150 mg/dL in the above study, respectively (20). So smoking remained as

the major causative factor of hypertriglyceridemia above the plasma triglycerides value of 200 mg/dL. Beside that, only cases with plasma triglycerides values lower than 60 mg/dL had a normal mean BMI (20). On the other hand, the triglycerides values increased about 8.1 mg/dL for each year of aging up to 200 mg/dL in the plasma (20) indicating that aging alone may be another risk factor for chronic low-grade inflammation on vascular endothelium in whole body. Although ATP III reduced the normal upper limit of plasma triglycerides as 150 mg/dL in 2001 (16), the above study indicated that lower limits provide additional benefits for human health (20). Similar to the recent study (43), prevalence of smoking was the highest in the highest triglycerides having group in the above study (20) that may also indicate the inflammatory role of smoking in the metabolic syndrome, since triglycerides may behave as acute phase reactants in the plasma. FPG, BMI, HT, DM, and COPD increased parallel to the increased plasma triglycerides in the above study, gradually (20). In our opinion, significantly increased mean age by the increased plasma triglycerides values may be secondary to aging-induced decreased physical and mental stresses, which eventually terminates with excess weight and its consequences. Interestingly, although the mean age increased from the lowest triglycerides having group up to the triglycerides value of 200 mg/dL, it then decreased. The similar trend was also seen with the mean LDL values. These trends may be due to the fact that although the borderline high triglycerides values (150-199 mg/dL) are 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 irreversible consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (16). 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 (20). Eventually, although some authors reported that lipid assessment can be simplified by measurements of TC (44), the present study and most of the others indicated significant relationships between LDL, HDL, and triglycerides values and irreversible end-points of the metabolic syndrome (19, 20, 45). Similar to the present study, the mean age, FPG, systolic and diastolic BP, TC, and HDL values gradually increased from the normal weight towards the overweight and obesity groups in the previous study (19).

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