What a low sensitivity of high density lipoproteins in the metabolic syndrome

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Abstract

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

Methods: Patients with plasma triglycerides lower than 60 mg/dL were put into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and 200 mg/dL or greater into the fifth groups, respectively.

Results: The study included 875 cases (370 males). Although the mean age increased just up to plasma triglycerides value of 200 mg/dL, the male ratio and smoking increased parallel to the increased plasma triglycerides values, continuously. Mean body mass index was only normal in patients with plasma triglycerides values lower than 60 mg/dL. Although fasting plasma glucose (FPG), hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and chronic renal disease (CRD) increased parallel to the increased plasma triglycerides values continuously, low density lipoproteins (LDL), white coat hypertension (WCH), and coronary heart disease (CHD) increased just up to plasma triglycerides value of 200 mg/dL. On the other hand, the mean HDL values were similar in all of the five groups ($p>0.05$ between all).

Conclusions: Plasma triglycerides may behave as acute phase reactants indicating disseminated endothelial injury and atherosclerosis in the metabolic syndrome. FPG, LDL, WCH, HT, DM, COPD, CHD, and CRD were all deteriorated parallel to the increased male ratio, smoking, aging, excess weight, and plasma triglycerides values. Whereas the mean HDL values did't show any significant change parallel to the above parameters in none of the groups.

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

Introduction

Chronic low-grade endothelial inflammation may be the most common kind of vasculitis, and the leading cause of aging in human being (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Probably whole afferent vasculature including capillaries are mainly involved in the process. Thus 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 natures, all of those reduce blood supply to the end-organs, and increase 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, peripheric 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 factors may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, stroke, or early aging, endothelial destructions can not be reversed effectively due to their fibrotic natures. 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). Similarly, plasma lipoprotein levels probably are under dynamic control, and they may act as some acute phase reactants indicating disseminated inflammation anywhere of the body. Although its normal limits could not been determined clearly yet, high plasma triglycerides may be significant indicators of the metabolic syndrome (14). 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). Although these cutpoints, there are several reports about the lower and safer limits of the triglycerides in the literature (18, 19). 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 significance of HDL in the metabolic syndrome in the present study.

Material 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 or body weight (20, 21). 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). CRD is diagnosed with a persistently elevated serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Additionally, office blood pressure (OBP) was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hour. 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 (22). 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 (22). 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% (23). Eventually, patients with plasma triglycerides values of lower than 60 mg/dL were put into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and 200 mg/dL or higher into the fifth groups, respectively. The mean age, male ratio, smoking,

BMI, FPG, triglycerides, LDL, HDL, WCH, HT, DM, COPD, CHD, and CRD 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 875 patients (505 females and 370 males), totally. The mean values of plasma triglycerides were 51.0, 78.3, 122.2, 174.1, and 325.8 mg/dL in the five groups, respectively. The mean age increased just up to the plasma triglycerides value of 200 mg/dL, and there was an increase of triglycerides about 7.8 mg/dL for each year of aging. Whereas the male ratio increased parallel to the increased plasma triglycerides values, continuously (30.9% versus 51.2%, p<0.001). Beside that the mean BMI values were 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five groups, respectively. In another word, only the cases with the plasma triglycerides values lower than 60 mg/dL had a normal mean BMI value. Although FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma triglycerides values continuously, LDL, WCH, and CHD increased just up to the plasma triglycerides value of 200 mg/dL. Prevalence of smoking increased parallel to the increased plasma triglycerides values, continuously (16.6% versus 38.3%, p<0.001). Interestingly, the most significant increase of smoking was seen just after the plasma triglycerides value of 200 mg/dL without the effects of aging or excess weight. On the other hand, the mean HDL values did't show any change between none of the five groups, significantly (p>0.05 between all) (Table 1).

Discussion

Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathophysiology of accelerated atherosclerotic process in whole body (24). 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-fourths of cases above the age of 30 years have excess weight, nowadays (24). It leads to structural and functional abnormalities in many organ systems of the body (25). 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 (26). 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 (27). 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 prevalences of CHD and stroke increased parallel to the increased BMI values in another study (28), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (29). The relationships between excess weight, increased BP, and higher plasma triglycerides values are described in the metabolic syndrome, extensively (14), and clinical manifestations of the syndrome include obesity, hypertriglyceridemia, hyperbetalipoproteinemia, HT, insulin resistance, and proinflammatory and prothrombotic states (12). Similarly, prevalences 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 another study (30). On the other hand, the prevalences of hyperbetalipoproteinemia were similar both in the hypertriglyceridemia (200 mg/dL or greater) and control groups (18.9% versus 16.3%, p>0.05, respectively) in the above study (30). Similarly, plasma LDL values increased just up to the plasma triglycerides value of 200 mg/dL in the present study. 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). According to 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, worldwide. According to our experiences, 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 the most clearly detected in the 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. 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 the 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 patients. Due to the very low prevalence of alcoholism in Turkey (31), 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 human and

Table 1: Characteristics features of the study cases according to the plasma triglycerides values

Variable	Lower than 60 mg/dL	p-value	Lower than 100 mg/dL	p-value	Lower than 150 mg/dL	p-value	Lower than 200 mg/dL	p-value	200 mg/dL or greater
Number of cases	84		207		235		148		201
Age (year)	35.6 ± 16.4 (17-79)	0.000	43.6 ± 17.5 (16-83)	0.009	47.7 ± 15.3 (16-82)	0.018	51.2 ± 12.6 (19-82)	Ns*	49.8 ± 12.3 (19-88)
Male:ratio	30.9%	0.05>	39.1%	Ns	40.4%	Ns	43.9%	0.05>	51.2%
Smoking	16.6%	Ns	21.7%	Ns	26.3%	Ns	23.6%	0.0001>	38.3%
BMI† (kg/m²)	24.6 ± 5.3 (16.7-45.9)	0.002	27.1 ± 5.9 (16.7-49.3)	0.000	29.4 ± 6.1 (18.4-51.0)	Ns	29.9 ± 4.8 (19.2-49.0)	Ns	30.0 ± 5.0 (21.0-51.1)
FPG‡ (mg/dL)	96.5 ± 35.3 (71-377)	0.016	106.6 ± 48.7 (59-400)	Ns	106.8 ± 35.1 (71-335)	0.006	117.3 ± 47.8 (68-386)	Ns	124.3 ± 55.3 (74-392)
Triglycerides (mg/dL)	51.0 ± 7.5 (27-59)	0.000	78.3 ± 10.8 (60-99)	0.000	122.2 ± 14.5 (100-149)	0.000	174.1 ± 14.2 (150-199)	0.000	325.8 ± 160.4 (200-1.350)
LDL§ (mg/dL)	98.6 ± 23.3 (56-161)	0.000	114.6 ± 33.0 (31-269)	0.000	131.1 ± 31.7 (56-228)	0.033	137.5 ± 32.4 (50-237)	0.020	129.0 ± 40.8 (10-239)
HDL‖ (mg/dL)	44.9 ± 12.3 (24-77)	Ns	48.8 ± 11.6 (33-91)	Ns	46.4 ± 10.5 (27-80)	Ns	43.7 ± 9.0 (22-67)	Ns	43.1 ± 9.1 (25-70)
WCH**	17.8%	0.05>	24.1%	0.05>	31.0%	Ns	35.1%	Ns	32.3%
HT***	8.3%	0.001>	15.9%	0.05>	21.2%	Ns	22.2%	Ns	26.3%
DM****	2.3%	0.001>	11.1%	Ns	13.6%	Ns	18.2%	0.05>	24.3%
COPD*****	4.7%	0.01>	9.1%	0.01>	14.0%	Ns	12.8%	0.05>	18.4%
CHD******	4.7%	0.001>	10.1%	Ns	11.4%	Ns	14.8%	Ns	11.9%
CRD*******	0.0%	Ns	1.9%	Ns	0.4%	0.01>	2.0%	0.01>	4.9%

*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 *******Chronic renal disease

nicotine administration in animals may be associated with a decreased BMI (32). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (33), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (34). According to an animal study, nicotine may lengthen intermeal time, and simultaneously decrease amount of meal eaten (35). Additionally, BMI seems to be the highest in former and lowest in current smokers (36). Smoking may be associated with a postcessation weight gain (37). Similarly, although CHD was detected with similar prevalences in both genders in a previous study (38), prevalences of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females. Additionally, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (39). 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 (40). 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 the cigarette smoke get into the circulation by means of the respiratory tract and lungs, and cause a vascular endothelial inflammation in whole body until the clearence from the circulation. But due to the repeated smoking habit of the individuals, the clearence 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 (34-36). After smoking cessation, appetite normalizes with a prominent weight gain but the returned weights are the patients' physiological weights, actually.

The prevalence of excess weight increases by decades, particularly after the third decade, up to the eight decade of life (24). So 30th and 70th years of age may be the breaking points of life for 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 for 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 present study, respectively. So smoking was remained as the major causative factor of the hypertriglyceridemia above the plasma triglycerides value of 200 mg/dL. Beside that, the mean BMI values were 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five study groups, respectively. In another word, only cases with the plasma triglycerides values lower than 60 mg/dL had a normal mean BMI value. On the other hand, the mean age and triglycerides of the first group were 35.6 years and 51.0 mg/dL, respectively. They were 43.6 years and 78.3 mg/dL in the second, 47.7 years and 122.2 mg/dL in the third, and 51.2 years and 174.1 mg/dL in the fourth groups, respectively. In another definition, the triglycerides values increased about 7.8 mg/dL for each year of aging up to 200 mg/dL in the plasma. So 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 present study indicate that lower limits provide additional benefits for human health. Similar to a recent study (41), prevalence of smoking was the highest in the highest triglycerides having group in the present study that may also indicate inflammatory role of smoking in the metabolic syndrome, since triglycerides may behave as acute phase reactants in the plasma. FPG, BMI, HT, DM, COPD, and CRD increased parallel to the increased plasma triglycerides values from the first up to the fifth groups, gradually in the present study. As one of our opinions, 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, then it 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) 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 genetic factors, smoking, 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, prevalences of HT, DM, and COPD were the highest in the highest triglycerides having group in the present study. Eventually, although some authors reported that lipid assessment can be simplified by measurements of TC (42), the present study and most of the others indicated a causal relationship between higher triglycerides values and irreversible end-points of the metabolic syndrome (19, 43). On the other hand, although FPG, systolic and diastolic BP, TC, HDL, triglycerides, and mean age increased from the normal weight towards the overweight and obesity groups continuously, LDL did not show a continuous increase in the previous study (19), and the increase of TC values may just be due to the increases of HDL and triglycerides in the plasma (19). Whereas we studied a larger patients' group, and did even not detect the increase of HDL values in the present study.

As a conclusion, plasma triglycerides may behave as acute phase reactants indicating disseminated endothelial injury and atherosclerosis in the metabolic syndrome. There may be significant associations between male gender, smoking, aging, excess weight, and plasma triglycerides values. FPG, LDL, WCH, HT, DM, COPD, CHD, and CRD were all deteriorated parallel to the increased male ratio,

smoking, aging, excess weight, and plasma triglycerides values. Whereas the mean HDL values did't show any significant change parallel to the above parameters in the present study.

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