SMOKING-INDUCED ENDOTHELIAL INJURY TRIGGERS PLASMA TRIGLYCERIDES

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Abstract

Background: We tried to understand whether or not smoking-induced endothelial injury triggers plasma triglycerides.

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, male ratio and smoking increased parallel to increased plasma triglycerides values, continuously. Interestingly, the most significant increase of smoking was seen just after plasma triglycerides value of 200 mg/dL, and there was no significant effect of aging or excess weight on this step. Mean body mass index (BMI) 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 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.

Conclusions: Plasma triglycerides may behave as acute phase reactants indicating disseminated endothelial injury and atherosclerosis. 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 all deteriorated parallel to the increased male ratio, smoking, mean age, BMI, and plasma triglycerides values.

Key words: Male gender, smoking, early aging, excess weight, hypertriglyceridemia

Introduction

Chronic endothelial injury may be the most common kind 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 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 endothelial injury, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature; all of those reduce blood supply to end-organs, and increase systolic BP further. Some of the well-known underlying causes and 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, chronic infections such as tuberculosis, and chronic inflammations such as rheumatologic disorders. Some of the irreversible consequences of the chronic 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, early aging, and premature death (5-7). Although early withdrawal of the causative factors may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, stroke, or aging, endothelial destruction cannot be reversed effectively due to their fibrotic nature. The triggering etiologies and terminal consequences of the chronic inflammatory process were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (8-11). Although its normal limits could not be determined clearly, higher plasma triglycerides values may be significant indicators of the metabolic syndrome (12). Due to the significant 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 (13, 14). Although ATP II determined the normal upper limit of triglycerides as 200 mg/dL in 1994, World Health Organisation in 1999 (15) and ATP III in 2001 reduced their normal upper limit to 150 mg/dL (14). Although these cutpoints are usually used to define borders of the metabolic syndrome, there is suspicion about the safest upper limit of plasma triglycerides in the literature. On the other hand, smoking may be one of the most common causes of vasculitis worldwide. It is a major risk factor for the development of atherosclerotic endpoints including CHD, PAD, COPD, cirrhosis, CRD, stroke, early aging, and premature death (16, 17). We tried to understand whether or not smoking-induced endothelial injury triggers plasma triglycerides values 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 year were included into the study. 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), high density lipoproteins (HDL), an electrocardiogram, and an abdominal ultrasonography were 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, or acarbose users were excluded to avoid their possible effects on blood lipid profiles or body weight (18, 19). 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 (14). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (14). 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 (14). 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 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 after a 10-minute education session about proper BP measurement techniques (20). 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 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 (20). 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 was diagnosed either angiographically or with the Doppler echocardiographic findings as the 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% (21). 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 greater 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 cases (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 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 study groups, respectively. In other words, only the cases with the plasma triglycerides values lower than 60 mg/dL had a normal mean BMI. 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. Mean HDL values were similar in all of the five groups interestingly ($p>0.05$ between all). 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, and there was no significant effect of aging or excess weight on this step (Table 1 - next page).

Discussion

Excess weight leads to structural and functional abnormalities in nearly all organ systems of the body (22). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines; all of those act as acute phase reactants in the plasma (23). 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 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. Beside that, FPG and total cholesterol increased parallel to the increased BMI (24). 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 another study (25), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (26). The relationships between excess weight, increased BP, and plasma triglycerides values were described in the metabolic syndrome, extensively (12), and clinical manifestations of the syndrome include obesity, hypertriglyceridemia, hyperbetalipoproteinemia, HT, insulin resistance, and proinflammatory and prothrombotic states (10). 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 another study (27). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia (200 mg/dL or higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (27). 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).

Smoking and alcohol have to be accepted as two of the major components of the metabolic syndrome since they cause chronic inflammations on the vascular endothelium, terminating with an accelerated atherosclerosis. Smoking'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 smoking are the 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. According to our clinical observations, although smoking 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 in general. Probably, alcohol causes harm to vascular endothelium in 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 in general. Due to the very low prevalence of alcoholism in Turkey, we did not include regular alcohol intake into the present study (28). On the other hand, smoking in humans and nicotine administration in animals may be associated with a decreased BMI (29). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (30), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (31). According to an animal study, nicotine may lengthen intermeal time and simultaneously decrease amount of meal eaten (32). Additionally, BMI seems to be the highest in former and lowest in current smokers (33). Smoking may be associated with a postcessation weight gain (34). Similarly, although CHD was detected with similar prevalences in both genders in a previous study (35), prevalence of smoking and COPD were higher in

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%	*0.001>*	*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

males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking (36). Similarly, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (37). In another definition, smoking may be more dangerous for women probably due to the higher BMI and its consequences in them. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (19). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. 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 via 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 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 appetite loss is an indicator of being ill instead of being healthy (31-33). After smoking cessation, appetite normalizes with a prominent weight gain in the patients but the returned weight is their physiological weights, actually.

Although the obvious consequences of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (38). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eighth decade of life (38). 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, respectively, in the present study. So smoking remained as the major causative factor for 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 other words, only the cases with the plasma triglycerides lower than 60 mg/dL had a normal mean BMI. 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 (14), whether or not much lower limits provide some additional benefits for the human body is unclear (39). Similar to a recent study (40), prevalence of smoking was the highest in the highest triglycerides having group in the present study 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, COPD, and CRD increased parallel to the plasma triglycerides values from the first up to the fifth groups, continuously in the present study. As an opinion, significantly increased mean age by the increased plasma triglycerides values may be secondary to aging-induced decreased physical and mental stresses, which eventually terminate 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. A 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 triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL or 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 (14). 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 present study. Eventually, although some authors reported that lipid assessment can be simplified by measurements of total cholesterol (41), the present study and most of the others indicated a causal relationship between higher triglycerides and irreversible end-points of the metabolic syndrome (42).

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

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