Smoking-induced endothelial damage may increase plasma triglycerides

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Abstract

Background: Smoking-induced endothelial damage may increase plasma triglycerides.

Methods: Patients with plasma triglycerides values lower than 60 mg/dL were collected 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 and higher into the fifth groups.

Results: The study included 669 cases (393 females), totally. Mean age increased just up to triglycerides value of 200 mg/dL, and there was an increase of triglycerides about 8.1 mg/dL for each year of aging up to this value. Male ratio increased parallel to the increased triglycerides, gradually (32.3% versus 50.0%, p<0.001). Body mass index (BMI) increased just up to plasma triglycerides of 150 mg/dL. Fasting plasma glucose, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease increased parallel to the increased triglycerides, gradually. Whereas low density lipoproteins and white coat hypertension increased just up to plasma triglycerides of 200 mg/dL. Prevalence of smoking increased parallel to the increased triglycerides, gradually (16.9% versus 39.1%, p<0.001). Interestingly, the most significant increase of smoking was seen after the triglycerides value of 200 mg/dL, and there was no significant effect of aging or excess weight on these patients.

Conclusions: Plasma triglycerides may actually be some acute phase reactants indicating disseminated endothelial damage, inflammation, fibrosis, and eventual atherosclerosis all over the body. There may be some significant relationships between the plasma triglycerides and aging, BMI, and smoking, but smoking may be particularly important for plasma triglycerides values of 200 mg/dL and greater.

Key words: Smoking, triglycerides, acute phase reactant, chronic endothelial damage, accelerated atherosclerosis

Introduction

Chronic endothelial damage may be the most common kind of vasculitis, and the leading cause of aging and death 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, and 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 endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature and reduce blood supply to terminal organs and increase 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), and chronic inflammatory processes including rheumatologic disorders, chronic infections, and cancers. 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, and stroke (5-9). Although early withdrawal of the causative factors may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature. The underlying causes and terminal consequences were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (10-13). Although its normal limits have not been determined clearly yet, higher plasma triglycerides may be significant indicators of the metabolic syndrome (14). Due to the strong association between higher plasma triglycerides and prevalence of CHD, the Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (15, 16). Although ATP II determined the normal triglycerides value as lower than 200 mg/dL in 1994, the World Health Organisation in 1999 (17) and ATP III in 2001 reduced its normal limit as lower than 150 mg/dL (15). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are suspicions about the safest limits of plasma triglycerides in medicine. Beside that, smoking may be found among one of the most common causes of vasculitis all over the world. It is a major risk factor for the development of atherosclerotic endpoints including CHD, PAD, COPD, cirrhosis, CRD, and stroke (18, 19). We tried to understand whether or not there is a significant relationship between smoking and 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 years were studied. Their medical histories including HT, DM, COPD, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglycerides, and low density lipoproteins (LDL) was performed. 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, 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 (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 (15). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (15). 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 (15). 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 normotensives in the office due to the risk of masked HT after a 10 minutes of 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 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 (22). 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 collected into the first, lower than 100 mg/dL into the second, lower than 1500 mg/dL into the third, lower than 200 mg/dL into the fourth, and 200 mg/dL and higher into the fifth groups. The mean age, male ratio, BMI, FPG, triglycerides, and LDL, and prevalence of smoking, WCH, HT, DM, and COPD 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 669 cases (393 females and 276 males), totally. The mean plasma triglycerides values of the groups were 51.0, 78.2, 121.8, 174,7, and 301.7 mg/dL, respectively. The mean age increased just up to the plasma triglycerides value of 200 mg/dL, and there was an increase of triglycerides about 8.1 mg/dL for each year of aging up to this value. Male ratio increased parallel to the increased plasma triglycerides values, gradually (32.3% versus 50.0%, p<0.001). BMI increased just up to the plasma triglycerides value of 150 mg/dL. FPG, HT, DM, and COPD increased parallel to the increased plasma triglycerides values, gradually, whereas LDL and WCH increased just up to the plasma triglycerides value of 200 mg/dL, gradually. Prevalence of smoking increased parallel to the increased plasma triglycerides values, gradually (16.9% versus 39.1%, 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 not any significant effect of aging or excess weight on these patients (Table 1).

Discussion

Excess weight may lead to both structural and functional abnormalities of many organ systems in the body. Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines which act as acute phase reactants in the plasma (24, 25). Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerotic process all over the 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. Beside this, the prevalence of high FPG and total cholesterol and low high density lipoproteins (HDL) increased parallel to the higher values of BMI (26). A combination of these cardiovascular risk factors will eventually terminate with an increase in left ventricular stroke work, higher risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the higher BMI values in the other studies (26, 27), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (28). The relationships between excess weight and increased BP and plasma triglycerides values were described in the metabolic syndrome (14), and clinical manifestations of the syndrome included obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (12). 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 (29). 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 (29). 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, significanty (p<0.05 for each step), but no more in the present study.

Smoking causes a chronic inflammatory process on the vascular endothelium, particularly on the respiratory tract and lungs, terminating with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Therefore smoking should be accepted as one of the major components of the metabolic syndrome. Strong and irreversible atherosclerotic effects of smoking are the most obvious observed in Buerger's disease (Thromboangiitis obliterans). It is an obliterative disease 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 medicine. Beside the strong atherosclerotic effects of smoking, smoking in the human body and nicotine administration in animals may be associated with a decreased BMI (30). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (31), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (32). According to an animal study, nicotine may lengthen intermeal time and simultaneously decrease amount of meal eaten (33). Additionally, BMI seems to be the highest in former and the lowest in current smokers (34). Smoking may be associated with a postcessation weight gain (35). Similarly, although CHD was detected with a similar prevalence in both genders in a previous study (36), prevalence of smoking and COPD were higher in males against the higher mean values or prevalence of the BMI, LDL, triglycerides, WCH, HT, and DM in females. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking (37). Similarly, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (38). In another definition, smoking is 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 (21). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. 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 disseminated inflammation in the body. Physicians can even understand healing of 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

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

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 higher
Number	65		158		188		110		148
Age (year)	36.1 ± 16.6 (17-79)	0.011	41.9 ± 17.0 (16-83)	0.001	47.1 ± 15.0 (16-82)	0.005	51.3 ± 12.0 (19-73)	Ns*	49.5 ± 11.6 (21-86)
Male ratio	32.3%	Ns	36.0%	Ns	40.4%	Ns	43.6%	Ns	50.0%
Smoking	16.9%	Ns	18.3%	0.05>	25.0%	Ns	24.5%	0.001>	39.1%
BMI† (kg/m2)	24.4 ± 4.5 (16.7-38.1)	0.003	27.0 ± 5.9 (16.7-49.3)	0.000	29.3 ± 6.0 (18.4-50.5)	Ns	29.9 ± 4.8 (19.2-49.0)	Ns	30.1 ± 5.1 (21.0-51.1)
FPG‡ (mg/dL)	98.5 ± 39.6 (77-377)	Ns	107.1 ± 52.0 (59-400)	Ns	104.7 ± 31.9 (71-327)	0.029	116.2 ± 48.5 (68-386)	Ns	122.0 ± 49.1 (74-338)
Triglycerides (mg/dL)	51.0 ± 7.7 (27-59)	0.000	78.2 ± 11.1 (60-99)	0.000	121.8 ± 14.9 (100-149)	0.000	174.7 ± 14.8 (150-199)	0.000	301.7 ± 108.7 (200-1.144)
LDL§ (mg/dL)	99.5 ± 23.4 (56-161)	0.02	114.4 ± 34.1 (43-269)	0.021	132.5 ± 31.2 (64-228)	Ns	138.8 ± 29.9 (50-210)	Ns	129.9 ± 38.7 (10-239)
WCH‖	16.9%	0.01>	25.3%	Ns	30.8%	Ns	34.5%	Ns	33.7%
HT**	6.1%	0.001>	12.6%	0.01>	20.7%	Ns	23.6%	Ns	24.3%
DM***	3.0%	0.001>	10.7%	Ns	13.2%	Ns	16.3%	0.01>	25.6%
COPD****	6.1%	Ns	9.4%	Ns	12.7%	Ns	13.6%	0.01>	22.9%

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

explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (32-34). After smoking cessation, normal appetite comes back with a prominent weight gain in the patients but the returned weight is their physiological weight, actually.

Although the obvious consequences of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (39). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eighth decade of life (39). 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 after the plasma triglycerides values of 200 mg/dL in the present study. On the other hand, the mean age and triglycerides value of the first group were 36.1 years and 51.0 mg/dL, respectively. They were 41.9 years and 78.2 mg/dL in the second, 47.1 years and 121.8 mg/dL in the third, and 51.3 years and 174.7 mg/dL in the fourth groups, respectively. In another definition, the triglycerides values increased about 8.1 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 all over the body. In this way, we may estimate the approximate age of patients by using their plasma triglycerides values below 200 mg/dL in the absence of any comorbid disorder or smoking.

Although ATP III reduced the normal border of plasma triglycerides as lower than 150 mg/dL in 2001 (15), whether or not much lower limits provide additional benefits for health is unclear. In the present study, prevalence of smoking was the highest in the highest triglycerides having group which may also indicate the inflammatory roles of smoking in the metabolic syndrome, since triglycerides may actually be some acute phase reactants in the plasma. The mean FPG and BMI and prevalence of HT, DM, and COPD increased parallel to the plasma triglycerides values from the first up to the last groups, gradually. As one of our opinions, significantly elevated mean age by the increased plasma triglycerides values may be secondary to aging-induced decreased physical and mental stresses, which eventually terminate with onset of excess weight and other components of the metabolic syndrome. 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 value. 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 triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL and higher) 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 (15). 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 and HDL (40), the present study and most of the others indicated a causal relationship between higher triglycerides and terminal consequences of the metabolic syndrome (41).

As a conclusion, plasma triglycerides may actually be some acute phase reactants indicating disseminated endothelial damage, inflammation, fibrosis, and eventual atherosclerosis all over the body. There may be some significant relationships between plasma triglycerides values and aging, BMI, and smoking, but smoking may be particularly important for plasma triglycerides values of 200 mg/dL and greater.

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