Triglycerides may behave as acute phase reactants in the plasma

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Abstract

Background: We tried to understand some unknown functions of 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 higher into the fifth groups, respectively.

Results: The study included 875 cases (505 females), totally. Mean age increased 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 values of triglycerides, continuously (30.9% versus 51.2%, p<0.001). Mean Body Mass Index (BMI) was 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five groups, respectively, and it was only normal in patients with plasma triglycerides values lower than 60 mg/dL. Fasting plasma glucose (FPG), hypertension (HT), diabetes mellitus (DM), smoking, chronic obstructive pulmonary disease (COPD), and chronic renal disease (CRD) increased parallel to the increased triglycerides, continuously. Whereas 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 damage, inflammation, fibrosis, and eventual atherosclerosis all over the body. Interestingly, parallel to the increased plasma triglycerides values, significant deterioration was observed regarding the components of the metabolic syndrome including mean age, male gender, smoking, BMI, FPG, LDL, WCH, HT, DM, COPD, CHD and CRD.

Key words: Triglycerides, acute phase reactants, smoking, male gender, excess weight, aging, chronic endothelial damage, accelerated atherosclerosis

Introduction

Chronic endothelial damage 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 inducing recurrent injuries on endothelium, and 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 damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature which reduces blood supply 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, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), chronic inflammatory or infectious processes, and cancers. Some of the irreversible consequences of the chronic destructive 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 (5-7). 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 literature, extensively (8-13). Although its normal limits have not been determined yet, higher triglycerides values may be significant indicators of the metabolic syndrome (14). Due to the strong association between higher plasma triglycerides and prevalence of CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (15, 16). Although ATP II determined the normal value of plasma triglycerides as lower than 200 mg/dL in 1994, World Health Organisation in 1999 (17) and ATP III in 2001 reduced its normal limit as lower than 150 mg/dL (16). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are suspicions about the safest upper limit of plasma triglycerides in the literature. We tried to understand some undetermined functions of plasma triglycerides 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 included into the study. Their medical histories including HT, DM, COPD, and already used medications were learnt, and a routine check up procedure was performed including fasting plasma glucose (FPG), creatinine, liver function tests, markers of hepatitis viruses A, B, C, and human immunodeficiency virus, plasma triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), an electrocardiogram, an abdominal ultrasonography, and a Doppler echocardiogram 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, acute or chronic renal failure, 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 and body weight (18, 19). Body mass index (BMI) of each patient was calculated by 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 higher 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 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 brief education 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 was performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography was 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). Finally, 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, female ratio, smoking, BMI, FPG, plasma triglycerides, LDL, HDL, WCH, HT, DM, COPD, CHD and CRD were detected in the five groups 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 triglycerides values 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. 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. As another definition, only the cases with plasma triglycerides values lower than 60 mg/dL had a normal mean BMI value. FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma triglycerides values, continuously. Whereas LDL, WCH, and CHD increased just up to the triglycerides value of 200 mg/dL. Although the prevalence of smoking increased parallel to the increased triglycerides values, continuously (16.6% versus 38.3%, p<0.001), the most significant increase was seen just after the plasma triglycerides value of 200 mg/dL, and there was no significant difference about the effects of aging or excess weight on this step. On the other hand, the mean HDL values were similar in all of the five groups; interestingly (p>0.05 between all) (Table 1).

Discussion

Excess weight may lead to 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 (22, 23). 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 that, the prevalence of high FPG and total cholesterol increased parallel to the higher values of BMI (24). 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 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 were described in the metabolic syndrome (14), and clinical manifestations of the syndrome included 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, although 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), the mean LDL values increased up to the plasma triglycerides value of 200 mg/dL but not more 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 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 (12, 13). 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. Thus smoking should be accepted as one of the major components of the metabolic syndrome. Strong and irreversible atherosclerotic effects of smoking are the most obviously observed 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. Beside the strong and irreversible atherosclerotic effects of smoking, smoking in humans and nicotine administration in animals may be associated with a decreased BMI (28). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (29) and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (30). According to an animal study, nicotine may lengthen intermeal time and simultaneously decrease amount of meal eaten (31). Additionally, BMI seems to be the highest in former and the lowest in current smokers (32). Smoking may be associated with a postcessation weight gain (33). Similarly, although CHD was detected with similar prevalence in both genders in a previous study (34), prevalence of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females with CHD. This result may indicate both the strong atherosclerotic and appetite decreasing roles of smoking (35). Similarly, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (36). In another definition, smoking is 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 (19). So smoking is a powerful atherosclerotic risk factor with suppressor effects on appetite. Smoking-induced appetite loss may be related with the 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 understand healing of their patients by means of 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. But due to the repeated smoking habit, the clearance

Table 1: Characteristic 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 higher
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 ± 145 (100-149)*	*0.000*	*174.1 ± 142 (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

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 (30-32). After smoking cessation, appetite normalizes with a prominent weight gain 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 (37). The prevalence of excess weight increases by decades, particularly after the third decade (37), and 30th and 70th years of age may be the breaking points of life for weight. Aging may be the major determiner factor of excess weight. Probably, relatively 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. Interestingly, the mean age and BMI values 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 24.4, 27.0, 29.3, 29.9 and 30.1 kg/m2 in the five study groups, respectively. In other words, only the cases with the plasma triglycerides values of lower than 60 mg/dL had a normal BMI. On the other hand, the mean age and triglycerides value 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 all over the body.

Although ATP III reduced the normal upper limit of plasma triglycerides as 150 mg/dL in 2001 (16), whether or not much lower limits provide additional benefits for health is unknown (38). Similar to a recent study (39), prevalence of smoking was the highest in the highest triglycerides having group in the present study that may also indicate inflammatory roles of smoking in the metabolic syndrome, since triglycerides may actually be acute phase reactants in the plasma. FPG, BMI, HT, DM and COPD increased parallel to the increased plasma triglycerides from the first up to the last groups, gradually. As one of our opinions, significantly elevated mean age by the increased plasma triglycerides may be secondary to aging-induced decreased physical and mental stresses, which eventually terminates with onset of excess weight and its consequences. Interestingly, although the mean age increased 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) are seen together with physical inactivity and overweight, the high triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL or higher) may be secondary to both genetic factors, smoking, and terminal 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 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, COPD, and CRD 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 (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 behave as acute phase reactants indicating disseminated endothelial damage, inflammation, fibrosis, and eventual atherosclerosis all over the body. Interestingly, parallel to the increased plasma triglycerides values, significant deteriorations were observed regarding components of the metabolic syndrome including mean age, male gender, smoking, BMI, FPG, LDL, WCH, HT, DM, COPD, CHD and CRD in the present study.

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