Triglycerides may be acute phase reactants which are not negatively affected by pathologic weight loss

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ABSTRACT

Background: Sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with atherosclerosis induced end-organ failures in early decades of life.

Methods: Consecutive patients with the SCD and controls were studied.

Results: The study included 363 patients with the SCD (169 females) and 255 age and gender-matched controls (119 females). Mean ages of the SCD patients were similar in males and females (31.1 versus 31.0 years, respectively, p>0.05). Although the body weight and body mass index (BMI) were significantly retarded in the SCD patients (59.9 versus 71.5 kg and 21.9 versus 25.6 kg/m2, respectively, p= 0.000 for both), the body heights were similar in both groups (164.9 versus 167.0 cm, p>0.05). Parallel to the retarded body weight, fasting plasma glucose (92.8 versus 97.6 mg/dL, p= 0.005), total cholesterol (121.4 versus 165.0 mg/dL, p= 0.000), low density lipoproteins (70.4 versus 102.4 mg/dL, p= 0.000), high density lipoproteins (26.0 versus 39.6 mg/dL, p= 0.000), systolic blood pressures (BP) (115.2 versus 122.6 |mmHg, p= 0.000), and diastolic BP (73.0 versus 86.6 mmHg, p= 0.000) were all lower in the SCD patients, significantly. Interestingly, only the triglycerides (TG) value was higher in the SCD patients (129.4 versus 117.3 mg/dL, p= 0.000), significantly. Similarly, the alanine aminotransferase value was not suppressed in the SCD patients, too (27.4 versus 27.3 U/L, respectively, p>0.05).

Conclusion: Plasma TG may be acute phase reactants indicating disseminated endothelial injury and accelerated atherosclerosis all over the body, and their plasma values are not negatively affected by pathologic weight loss.

Key words: Sickle cell diseases, chronic endotelial damage, atherosclerosis, triglycerides, acute phase reactants, metabolic syndrome, body weight

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1, 2). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. 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 medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, and eventually reduce blood supply to the terminal organs, and increase systolic BP further. Some of the well-known accelerating factors or indicators of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (3, 4). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (5, 6). Although their normal limits have not been determined clearly yet, high plasma triglycerides (TG) values may be significant indicators of the metabolic syndrome (7). Due to the significant association between high plasma TG values and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for TG abnormalities than did ATP II (8, 9). Although ATP II determined the normal upper limit of TG as 200 mg/dL in 1994, World Health Organisation in 1999 (10) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (9). Although these cutpoints are usually used to define borders of the metabolic syndrome, there are suspicions about the safest upper limit of the TG in the plasma. On the other hand, sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (11, 12). Hemoglobin S (Hb S) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia in the whole body (13, 14). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the hard cells into the tissues. The hard RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early decades of life. Vascular narrowings and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in the SCD (16).

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University on consecutive patients with the SCD and routine check up cases between March 2007 and June 2016. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography. Medical histories of the SCD patients were learnt. A complete physical examination was performed by the same internist. Body mass index (BMI) of each case was calculated by the measurements of the same internist instead of by verbal expressions. Weight in kilograms is divided by height in meter squared (9). Systolic and diastolic BP were checked after a 5-minute rest in seated position using the mercury sphygmomanometer (ERKA, Germany), and no smoking was permitted during the previous 2 hours. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including fasting plasma glucose (FPG), total cholesterol (TC), high density lipoproteins (HDL), TG, serum creatinine, alanine aminotransferase (ALT), markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, and an electrocardiogram were performed. Eventually, the mean body weight, height, BMI, FPG, TC, low density lipoproteins (LDL), HDL, TG, ALT, and systolic and diastolic BP 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 363 patients with the SCD (169 females) and 255 control cases (119 females). Mean ages of the SCD patients were similar in males and females (31.1 versus 31.0 years, respectively, $p>0.05$). Although the mean body weight and BMI were retarded in the SCD patients, significantly (59.9 versus 71.5 kg and 21.9 versus 25.6 kg/m2, respectively, $p= 0.000$ for both), the mean body heights were similar in both groups (164.9 versus 167.0 cm, $p>0.05$). Parallel to the retarded mean body weight, FPG (92.8 versus 97.6 mg/dL, $p= 0.005$), TC (121.4 versus 165.0 mg/dL, $p= 0.000$), LDL (70.4 versus 102.4 mg/dL, $p= 0.000$), HDL (26.0 versus 39.6 mg/dL, $p= 0.000$), systolic BP (115.2 versus 122.6 mmHg, $p= 0.000$), and diastolic BP (73.0 versus 86.6 mmHg, $p= 0.000$) were all lower in the SCD patients, significantly. Interestingly, only the mean TG value was higher in the SCD patients (129.4 versus 117.3 mg/dL, $p= 0.000$), significantly. Similarly, the mean ALT value was not suppressed in the SCD patients, too (27.4 versus 27.3 U/L, respectively, $p>0.05$) (Table 1).

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	*p*-value	Control cases
Number	363		255
Mean age (year)	31.0 ±9.2 (17-59)	Ns†	31.2 ±8.6 (16-45)
Female ratio	46.5% (169)	Ns	46.6% (119)
Weight (kg)	59.9 ± 11.8 (30-122)	0.000	71.5 ± 16.4 (40-128)
Height (cm)	164.9 ±9.1 (142-194)	Ns	167.0 ±8.6 (147-192)
BMI‡ (kg/m^2)	21.9 ± 3.6 (14.3-46.4)	0.000	25.6 ± 5.8 (15.8-53.5)
FPG§ (mg/dL)	92.8 ± 12.5 (57-125)	0.005	97.6 ± 19.7 (66-269)
TC‖ (mg/dL)	121.4 ± 32.2 (65-296)	0.000	165.0 ± 54.3 (72-510)
LDL¶ (mg/dL)	70.4 ± 28.4 (20-270)	0.000	102.4 ± 41.1 (29-313)
HDL** (mg/dL)	26.0 ± 9.4 (4-60)	0.000	39.6 ± 13.2 (7-95)
*TG*** (mg/dL)*	*129.4 ± 90.4 (31-1216)*	*0.000*	*117.3 ± 107.4 (24-931)*
ALT**** (U/L)	27.4 ±16.2 (4-118)	Ns	27.3 ±21.6 (6-117)
Systolic BP***** (mmHg)	115.2 ± 15.7 (80-190)	0.000	122.6 ± 19.4 (80-200)
Diastolic BP (mmHg)	73.0 ± 12.3 (50-120)	0.000	86.6 ± 13.6 (60-120)

***Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index §Fasting plasma glucose ‖Total cholesterol ¶Low density lipoproteins **High density lipoproteins ***Triglycerides ****Alanine aminotransferase *****Blood pressures**

Discussion

SCD can affect all vascular organ systems of the body (17, 18). Aplastic crises, sequestration crises, hemolytic crises, acute chest syndrome, avascular necrosis of the femoral and humeral heads, priapism and infarction of the penis, osteomyelitis, acute papillary necrosis of the kidneys, CRD, occlusions of retinal arteries and blindness, pulmonary HT, bone marrow necrosis induced dactilitis in children, chronic punched-out ulcers around ankles, hemiplegia, and cranial nerve palsies are only some of the several presentation types of the SCD. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature (16). Delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies may decrease the expected survival time in the SCD patients further (19). Actually, RBC supports must be given immediately during all medical or surgical procedures in which there is evidence of clinical deterioration in the SCD (20). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling induced endothelial damage and inflammation all over the body. Due to the great variety of clinical presentation types, it is not surprising to see that the mean body weight and BMI were significantly retarded in patients with the SCD in the present study. On the other hand, as an opposite finding to some other reports (21, 22), the body heights were similar in patients with the SCD and control cases, here. Probably due to the significantly lower mean body weight and BMI, mean values of the FPG, TC, LDL, HDL, systolic BP, and diastolic BP were also lower in patients with the SCD, which can be explained by definition of the metabolic syndrome (23, 24).

Cholesterol, TG, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. TG are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of fat tissue deposited all over the body is in the form of TG. Phospholipids are TG that are covalently bound to a phosphate group. Phospholipids regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, TG, and phospholipids do not circulate freely in the plasma instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL in the plasma. Chylomicrons carry exogenous TG from intestine to liver via the thoracic duct. VLDL are produced in the liver, and carry endogenous TG from the liver to the peripheral organs. In the capillaries of adipose and muscle tissues, 90% of TG is removed by a specific group of lipases. So VLDL are converted into IDL by removal of TG. Then IDL are degraded into LDL by removal of more TG. So VLDL are the main sources of LDL in the plasma. LDL deliver cholesterol from the liver to other parts of the body. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors on macrophages which may migrate into arterial walls and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells, including within arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs including adrenals, ovaries, and testes for excretion, reutilization, and disposal. All of the carrier lipoproteins in the plasma are under dynamic control, and are readily affected by diet, illness, drug, body weight, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic

syndrome alone is a low-grade inflammatory process on vascular endothelial cells all over the body. Thus the metabolic syndrome alone may be a cause of the abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called 'the good cholesterol' due to their roles in removing excess cholesterol from the blood, and protecting the arterial walls against atherosclerosis (25), recent studies did not show similar results, and low plasma HDL levels may alert clinicians about searching for additional metabolic or inflammatory pathologies in the body (26, 27). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (27). However, HDL may become 'dysfunctional' in pathological conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (26). For instance, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation as well as the transformation of HDL proteomes into proinflammatory proteins. Additionally, the highly effective agents of increasing HDL levels such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (28). While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health (28). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL values may not increase cardiovascular health (28). So they may just be some indicators instead of being the main actors of the process. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD (29). Similarly, BMI, FPG, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence of DM was only 3.1% between these values against 22.2% of outside of these limits (30). In another definition, the moderate HDL values may also be the results instead of the causes of the better health parameters.

Probably excess weight may be the most common cause of vasculitis, worldwide, and the leading cause of major health problems in this century. It leads to structural and functional abnormalities in many organ systems of the body (31). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, all of which behave as acute phase reactants in the plasma (32). Excess weight induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathophysiology of disseminated atherosclerosis in whole body (1, 2). On the other hand, 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. Similar to the present study, FPG and TC values increased parallel to the increased BMI values (33). Combination of these cardiovascular risk factors will eventually terminate with an increased left ventricular stroke work and higher risks of arrhythmias, cardiac failure, and sudden death. Additionally, the prevalence of CHD and stroke increased parallel to the increased BMI values in another study (34), and risk of death from all causes including cancers increased throughout the range of moderate to severe excess weight in all age groups (35). The relationships between excess weight, increased BP, and higher plasma TG values were described in the metabolic syndrome, extensively (36), and clinical manifestations of the syndrome include obesity, hypertriglyceridemia, hyperbetalipoproteinemia, HT, insulin resistance, and proinflammatory and prothrombotic states (36). 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 (37). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (37). Similarly, plasma LDL values increased just up to the plasma TG value of 200 mg/dL but no more in another study (38). Beside that, the mean BMI values increased just up to the plasma TG value of 150 mg/dL, significantly ($p<0.05$ for each step) (38). On the other hand, the greatest number of deteriorations in the metabolic parameters were observed just above the plasma TG value of 60 mg/dL (38). 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.

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 body weight, and aging may be the major determining factor of excess weight. 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 at these ages. Interestingly, the mean age and BMI increased just up to the plasma TG values of 200 mg/dL and 150 mg/dL in the above study, respectively (38). So smoking remained as the major underlying factor for the hypertriglyceridemia above the plasma TG 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 (38). In other words, only cases with the plasma TG values lower than 60 mg/dL had a normal mean BMI value (38). On the other hand, the mean age and TG value of the first group were 35.6 years and 51.0 mg/dL, respectively (38). 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 (38). In another definition, TG values increased about 7.8 mg/dL for each year of aging up to 200 mg/dL in the plasma (38). 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 TG as 150 mg/dL in 2001 (9), whether or not much lower limits provide some additional benefits for human body remains unclear (40). Similar to the recent study (41), prevalence of smoking was the highest in the highest TG having group in the above study (38) which may also indicate the inflammatory role of smoking on vascular endothelium in the metabolic syndrome,

since TG may behave as acute phase reactants in the plasma. BMI, FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma TG values from the first up to the fifth groups, continuously in the above study (38). In out opinion significantly increased mean age by the increased plasma TG 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 TG having group up to TG value of 200 mg/dL, then it decreased (38). The similar trend was also seen with the mean LDL values (38). These trends may be due to the fact that although the borderline high TG values (150-199 mg/dL) are seen together with physical inactivity and overweight, the high TG (200-499 mg/dL) and very high TG values (500 mg/dL or higher) may be secondary to genetic factors, smoking, and terminal consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (9). But although the underlying causes of the high and very high plasma TG 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 TG having group in the above study (38). 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 TG values and irreversible end-points of the metabolic syndrome (43).

As a conclusion, plasma TG may be acute phase reactants indicating disseminated endothelial injury and accelerated atherosclerosis all over the body, and their plasma values are not negatively affected by pathologic weight loss.

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