BODY WEIGHT AND PLASMA LIPOPROTEINS

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Abstract

Background: Body weight may have some effects on plasma lipoproteins.

Methods: The study was performed in the Hematology and Internal Medicine Polyclinics on patients with sickle cell diseases (SCD) and routine check up cases.

Results: The study included 122 patients with the SCD (58 females) and 176 age and sex-matched control cases, totally. Mean age of patients with the SCD was 28.6 years. The mean body weight and body mass index were significantly retarded in patients with the SCD (71.6 versus 57.8 kg and 24.9 versus 20.7 kg/m2, respectively, p= 0.000 for both), whereas the mean body heights wasere similar in both groups (166.1 versus 168.5 cm, p>0.05). Parallel to the retarded mean body weight, mean values of the low density lipoproteins (LDL), high density lipoproteins (HDL), and alanine aminotransferase were also lower in patients with the SCD, significantly (p= 0.000 for all). Parallel to the retarded mean body weight again, mean values of the systolic and diastolic blood pressures were significanly lower in patients with the SCD (113.3 versus 118.8 and 72.3 versus 83.6 mmHg, respectively, p<0.01 for both).

Conclusion: Body weight may be the major determining factor of LDL and HDL values in the plasma.

Key words: Body weight, body mass index, low density lipoproteins, high density lipoproteins, metabolic syndrome

Introduction

Chronic endothelial damage may be the most common cause of end-organ insufficiency, early aging, and premature death in human beings (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying mechanism by inducing recurrent injuries on vascular endothelium. 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. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, which eventually reduces blood supply to the terminal organs and increases systolic BP further. Some of the well-known causes or signals 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, or 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, early aging, and premature death (5-7). Although early withdrawal of the underlying causes can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and early aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The underlying causes and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (8, 9). On the other hand, sickle cell diseases (SCD) are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (10, 11). 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 main pathology since sickling is rare in peripheric blood samples of the patients with associated thalassemia minor, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammation, infections, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body (12, 13). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (14), since the capillary system is the main distributor of the hard RBC into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in younger ages of the patients. Vascular occlusions induced 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 (15).

Material and Methods

The study was performed in the Hematology and Internal Medicine Polyclinics of the Mustafa Kemal University on patients with the SCD and routine check up cases between March 2007 and April 2010. Only patients with the SCD on silent phase instead of the patients with painful crises were included into the study. SCD were diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. The control cases were age and sex-matched cases with the SCD. The medical history of all cases including already used medications was learnt, and a routine check up procedure including fasting plasma glucose (FPG), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides, and alanine aminotransferase (ALT) values was performed. Body weight and height were measured, and body mass index (BMI) of each case was calculated by the same physician. Weight in kilograms is divided by height in meters squared (16). Systolic and diastolic BP were checked after a 5 minute rest in seated position by using the mercury sphygmomanometer (ERKA, Germany) with the same physician again, and no smoking was permitted during the previous 2 hours. Eventually, the mean body weight, height, BMI, FPG, LDL, HDL, triglycerides, 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 122 patients with the SCD (58 females) and 176 age and sex-matched control cases (84 females), totally. The mean age of patients with the SCD was 28.6 years. When we compared the patients and control groups, the mean body weight and BMI were significantly retarded in patients with the SCD (71.6 versus 57.8 kg and 24.9 versus 20.7 kg/m2, respectively, p= 0.000 for both), whereas the mean body heights were similar in both groups (166.1 versus 168.5 cm, p>0.05). The mean values of the FPG were unchanged between the patients and control groups (93.9 versus 94.7 mg/dL, respectively, p>0.05), and the mean value of triglycerides was higher in patients with the SCD, but the difference was nonsignificant (120.1 versus 112.1 mg/dL, p>0.05). Parallel to the retarded mean body weight and BMI, the mean values of LDL (74.0 versus 109.6 mg/dL), HDL (24.4 versus 42.6 mg/dL), and ALT (34.9 versus 56.7 U/L) were also lower in patients with the SCD, significantly (p= 0.000 for all). Parallel to the retarded mean body weight again, mean values of the systolic and diastolic BP were significantly lower in patients with the SCD (113.3 versus 118.8 and 72.3 versus 83.6 mmHg, respectively, p<0.01 for both) (Table 1). On the other hand, six patients with the SCD (three females and three males with mean ages of 32.3 and 29.3 years, respectively) were lost due to intercurrent infections induced sepsis, and there were pulmonary HT in two, cirrhosis in two, and cirrhosis plus CRD in one of them. Additionally, all of the lost six patients were Hb SS in nature.

Table 1: Characteristic features and metabolic parameters of the study cases

Variables	Sickle cell patients	*p*-value	Control cases
Number	122		176
Female ratio	47.5% (58)	Ns*	47.7% (84)
Age (year)	28.6 ± 10.2 (14-59)	Ns	28.6 ± 8.2 (15-58)
Weight (kg)	*57.8 ± 11.0 (31-83)*	*0.000*	*71.6 ± 14.4 (43-111)*
Height (cm)	166.1 ± 9.1 (145-188)	Ns	168.5 ± 10.0 (137-195)
BMI† (kg/m²)	*20.7 ± 2.9 (14.7-29.9)*	*0.000*	*24.9 ± 4.3 (17.3-41.2)*
FPG‡ (mg/dL)	93.9 ± 13.8 (56-119)	Ns	94.7 ± 12.0 (63-160)
LDL§ (mg/dL)	*74.0 ± 29.8 (24-164)*	*0.000*	*109.6 ± 29.6 (43-231)*
HDL‖ (mg/dL)	*24.4 ± 7.8 (9-45)*	*0.000*	*42.6 ± 11.0 (24-91)*
Triglycerides (mg/dL)	120.1 ± 63.9 (31-348)	Ns	112.1 ± 65.0 (27-388)
ALT¶ (U/L)	*34.9 ± 20.5 (11-125)*	*0.000*	*56.7 ± 26.6 (20-168)*
*Systolic BP** (mmHg)*	*113.3 ± 14.9 (80-150)*	*0.008*	*118.8 ± 16.6 (80-170)*
Diastolic BP (mmHg)	*72.3 ± 9.9 (60-100)*	*0.000*	*83.6 ± 10.7 (60-110)*

*Nonsignificant (p>0.05) †Body mass index ‡Fasting plasma glucose §Low density lipoproteins ‖High density lipoproteins ¶Alanine aminotransferase **Blood pressure

Discussion

Cholesterol, triglycerides, 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. Triglycerides are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of our body's fat tissue is in the form of triglycerides. Phospholipids are triglycerides 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, triglycerides, 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 triglycerides from intestine to liver via the thoracic duct. VLDL are produced in liver, and carry endogenous triglycerides from the liver to the peripheral organs including adipocytes and muscle tissue. In the capillaries of adipocytes and muscle tissue, 90% of triglycerides are removed by a specific group of lipases. So VLDL are converted into IDL by removal of triglycerides. Then IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma. LDL deliver cholesterol from the liver to the parts of 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 artery wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs such as adrenals, ovaries, and testes for excretion, re-utilization, and disposal. All of the carrier lipoproteins in the plasma are under dynamic control, and are readily affected by diet, illnesses, drugs, 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 endothelium 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 role in removing excess cholesterol from the blood and protecting the arterial walls against atherosclerosis (17), recent studies did not show similar results, and low plasma HDL levels may alert searching of additional metabolic or inflammatory pathologies in the body (18-20). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (18). However, HDL may become 'dysfunctional' in pathological conditions which means that relative composition of lipids and proteins, as well as the enzymatic activities of HDL are altered (18). For example, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation of HDL, as well as the transformation of HDL proteomes into proinflammatory proteins. Additionally, the highly effective agents of increasing HDL levels including niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (21). While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health (21). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL values may not increase cardiovascular health (21). So they may actually be just 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 (22). Similarly, BMI, FPG, DM, and CHD were the lowest between HDL values of 40 and 46 mg/dL, and the prevalence of DM was only 3.1% between these values against 22.2% of the others in another study (23). In another definition, the moderate HDL values may also be a result instead of a cause of the better health parameters. On the other hand, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma triglycerides value of 60 mg/dL in another study (24).

Excess weight may be the main cause of metabolic syndrome in the world, nowadays. Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, acting as acute phase reactants in the plasma (25). Excess weight-induced chronic low-grade vascular endothelial inflammation plays a significant role in the pathogenesis of accelerated atherosclerosis in the whole body (26). Additionally, excess weight leads to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors eventually terminate with increased risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI in the other studies (27, 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 relationship between excess weight, elevated BP, and hypertriglyceridemia is described in the metabolic syndrome, and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (30). Similarly, prevalence of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in another study (31).

Increased BP may result from a complex interaction of genes and environmental factors. Increased BP may be a sign that heart and blood vessels are being overworked. In most people with HT, increased total peripheral resistance accounts for HT while cardiac output remains normal (32). The increased peripheral resistance is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction in the number of capillaries may also contribute (33). HT is rarely accompanied by symptoms in the short-term. Symptoms attributed to HT may actually be related with associated anxiety rather than HT itself. However, HT may be a major risk factor for CHD, PAD, CRD, cirrhosis, COPD, stroke, and dementia-like end-organ insufficiencies in the long-term. For example, a reduction of the BP by 5 mmHg can decrease the risk of stroke by 34% and CHD by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular diseases (34). On the other hand, we cannot detect any absolute cause in the majority of patients with HT. Physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be important as the causes of HT in them, actually.

SCD include a group of genetic disorders characterized by the presence of Hb S, which was the first discovered hemoglobinopathy in the world (35). Together with hemoglobin E, it is the most common hemoglobinopathy at the moment. Hb S causes RBC to change their normal biconcave disc shape to a crescent or sickle shape during various stresses. The RBC can take their normal shapes after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they are damaged permanently, and hemolysis occurs. So lifespan of the RBC decreases from the normal 120 days to 15-25 days. This hemolysis is responsible for the anemia that is the hallmark of the SCD. Painful crises are the most disabling symptoms of the SCD. Although painful crises may not be life threatening directly (36), infections are the most common triggering factors of the crises. So the risk of mortality is significantly higher during the crises according to our experiences. On the other hand, the severe pain may be the result of a complex interaction between RBC, endothelium, white blood cells (WBC), and platelets. Probably, leukocytosis contributes to the pathogenesis of the painful crises by releasing several cytotoxic enzymes. The adverse actions of WBC on endothelium are of particular interest with regard to the stroke and cerebrovascular diseases in the SCD. For example, leukocytosis in the absence of any infection was an independent predictor of the severity of the SCD in a previous study (37), and it was associated with an increased risk of stroke in a cohort of Jamaican patients (38). Occlusions in vasculature of the bone marrow, bone infarctions, inflammatory mediators, and activation of

afferent nerves may take a role in the pathophysiology of the severe pain. Due to the severity of pain, narcotic analgesics are usually required (39). According to our experiences, the painful crises are the most disturbing problems for the patients, for their families, for health professionals, and even for other patients due to the severity and prolonged nature of the episodes.

Due to the repeated infarctions and subsequent fibrosis, the spleen is usually very small in adults. Eventually, a functional and anatomic asplenism develops due to the decreased antibody production, opsonization, and reticuloendothelial functions. Terminal consequence of the asplenism is increased risk of infections with Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis-like encapsulated bacteria. Particularly, pneumococcal infections are common in early childhood, and are associated with a high mortality rate. The causes of death were infection in 56% of infants in a previous study (37). In another study, the peak incidence of death among children with the SCD occured between 1 and 3 years of age, and the deaths under the age of 20 years were predominantly caused by pneumococcal sepsis (40). Adult patients, even those who appear relatively fit, are susceptible to sepsis, acute multiorgan failures, and sudden death during acute painful crises due to the severe immunosuppression in them.

SCD can affect nearly all organ systems of the body (41-43). 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 kidneys, CRD, occlusion 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 presentation types of the SCD. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature (15), whereas they were 29.3 and 32.3 years, respectively, in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Antakya region of Turkey (44). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (45). RBC supports decrease sickle cell concentration in circulation, and suppress bone marrow in 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 (46-47), the mean body height was 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 LDL, HDL, ALT, and systolic and diastolic BP were also lower in patients with the SCD, which can be explained by definition of the metabolic syndrome (48-51).

As a conclusion, body weight may be the major determining factor of LDL and HDL values in the plasma.

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