BODY MASS INDEX MAY BE THE MAJOR DETERMINING FACTOR OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN THE HUMAN BODY

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Received: December 2020; Accepted: January 2021; Published: February 1, 2021
Citation: Mehmet Rami Helvaci et al. Body mass index may be the major determining factor of systolic and diastolic blood pressure in the human body. Middle East Journal of Nursing 2021; 15(1): 12-17.
DOI: 10.5742/MEJN2021.93797

Abstract

Background: We tried to understand possible effects of sickle cell diseases (SCD) on metabolic parameters including systolic and diastolic blood pressure (BP) in the body.

Methods: All patients with the SCD and age and gender-matched control cases were included into the study.

Results: We studied 363 patients with the SCD (194 males) and 255 control cases (136 males), totally. 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 body mass index (BMI) were significantly suppressed 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 mean body heights were similar in both groups (164.9 versus 167.0 cm, p>0.05). Parallel to the suppressed mean body weight and BMI, 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), and high density lipoproteins (26.0 versus 39.6 mg/dL, p= 0.000) were all lower in the SCD patients, significantly. Similarly, both systolic (115.2 versus 122.6 mmHg, p= 0.000) and diastolic BP (73.0 versus 86.6 mmHg, p= 0.000) were also lower in them, significantly. Interestingly, only the mean triglycerides value was higher in the SCD patients (129.4 versus 117.3 mg/dL, p= 0.000), significantly. Similarly, mean alanine aminotransferase value was not suppressed in them, too (27.4 versus 27.3 U/L, p>0.05).

Conclusion: BMI may be the major determining factor of systolic and diastolic BP in the human body.

Key words: Body mass index, systolic blood pressure, diastolic blood pressure, metabolic syndrome, sickle cell diseases

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in the human body (1, 2). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term 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, and this eventually reduces blood supply to the terminal organs, and increases systolic BP further. Some of the well-known triggering causes or signs 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, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, stroke, dementia, various end-organ insufficiencies, aging, and death (3, 4). Although early withdrawal of the triggering causes can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, various end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The triggering causes and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (5, 6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and shortened survival in both genders (7, 8). 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 problem because sickling is rare in peripheric blood samples of 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, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (9, 10). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (11), 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 much younger ages of the patients. 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 patients (12). Actually, the SCD and metabolic syndrome may have similar pathophysiologic effects on the human body, and SCD are a chance for us to see several consequences of metabolic syndrome on the human body in much earlier ages of the patients. We tried to understand possible effects of the SCD on metabolic parameters including systolic and diastolic BP in the present study.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University on all patients with the SCD and age and gender-matched control 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 kilogram is divided by height in meter squared (13). Systolic and diastolic BP were checked after a 5-minute rest in seated position by 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. A check up procedure including fasting plasma glucose (FPG), total cholesterol (TC), high density lipoproteins (HDL), triglycerides (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 was 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 (194 males) and 255 control cases (136 males), totally. The 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 significantly suppressed 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 mean body heights were similar in both groups (164.9 versus 167.0 cm, p>0.05). Parallel to the suppressed mean body weight and BMI, 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), and HDL (26.0 versus 39.6 mg/dL, p= 0.000) were all lower in the SCD patients, significantly. Similarly, both systolic (115.2 versus 122.6 mmHg, p= 0.000) and diastolic BP (73.0 versus 86.6 mmHg, p= 0.000) were also lower in them,

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, mean ALT value was not suppressed in them, too (27.4 versus 27.3 U/L, p>0.05) (Table 1).

Discussion

Higher BP indicates that heart and blood vessels are being overworked. In most people with HT, increased peripheral vascular resistance accounts for HT while cardiac output remains normal (14). The increased peripheral vascular resistance is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction in the number of capillaries may also contribute (15). HT is rarely accompanied by symptoms in the short-term. Symptoms attributed to HT in that period may actually be related to associated anxiety rather than HT itself. However, HT may be the major risk factor for CHD, CRD, cirrhosis, COPD, stroke, dementia, and PAD-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 (16). 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 found among the possible risk factors of HT. Particularly, excess weight may be the major underlying cause of HT in the world, now. Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, acting as acute phase reactants in the plasma (17). Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerosis in the human body (18). Additionally, excess weight leads to myocardial hypertrophy terminating with a decreased cardiac compliance. A combination of these cardiovascular risk factors eventually terminate with increased risks of arrhythmias, cardiac failure, and sudden death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI in other studies (19, 20), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (21). 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 (22). Similarly, prevalences of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in another study (23). On the other hand, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma TG value of 60 mg/dL in another study (24). Interestingly, plasma TG were the only lipids that were not suppressed parallel to the suppressed body weight and BMI in the SCD patients in the present study.

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 that 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 endothelium all over the body. Thus the metabolic syndrome alone may be a cause of the abnormal lipoprotein levels in the plasma. Similarly, due to the severe inflammatory nature of the SCD, plasma TC (121.4 versus 165.0 mg/dL, p<0.000) and LDL values (70.4 versus 102.4 mg/dL, p<0.000) were suppressed parallel to the suppressed mean body weight (59.9 versus 71.5 kg, p<0.000) and BMI (21.9 versus 25.6 kg/m2, p<0.000) in the present study. 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. Instead, low plasma HDL values should alert clinicians about searching for additional metabolic or inflammatory pathologies in the human body (26, 27). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (26). However, HDL may become 'dysfunctional' in pathologic conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (26). For example, 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

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	*p*-value	Control cases
Number	363		255
Age (year)	31.0 ± 9.2 (17-59)	Ns†	31.2 ± 8.6 (16-45)
Male ratio	53.4% (194)	Ns	53.3% (136)
Body weight (kg)	*59.9 ± 11.8 (30-122)*	*0.000*	*71.5 ± 16.4 (40-128)*
Body height (cm)	164.9 ± 9.1 (142-194)	Ns	167.0 ± 8.6 (147-192)
BMI‡ (kg/m²)	*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 pressure

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 in human health. 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 DM was only 3.1% between these values against 22.2% outside of these limits (30). In another definition, the moderate HDL values may also be the results instead of causes of better human health. Similarly, plasma HDL value was suppressed significantly (39.6 versus 26.0 mg/dL, p<0.000) parallel to the suppressed mean body weight and BMI in the patients, probably due to the severe inflammatory nature of the SCD in the present study.

SCD are inherited hemolytic anemias characterized by the presence of Hb S, which was the firstly discovered hemoglobinopathy in the world (31). Together with hemoglobin E, it is the most common hemoglobinopathy known. Hb S causes RBC to change their normal biconcave disc shape to a 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, hemolysis occurs. So lifespan of the RBC decreases from the normal 120 days to 15-25 days. The chronic hemolytic anemia is mainly 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 (32), infections are the most common triggering factors of the crises. So the risk of mortality is significantly higher during the crises. On the other hand, the severe pain may be the result of complex interactions between RBC, white blood cells (WBC), platelets (PLT), and endothelial cells. Probably, leukocytosis contributes to the pathogenesis by releasing several cytotoxic enzymes. The adverse actions of WBC and PLT on the endothelial cells are of particular interest with regard to stroke and cerebrovascular diseases in the SCD (33). For example, leukocytosis in the absence of any infection was an independent predictor of the severity of the SCD (34), and it was associated with an increased risk of stroke (35). Occlusions of vasculature of the bone marrow, bone infarctions, inflammatory mediators, and activation of afferent nerves may take role in the pathophysiology of the severe pain. Due to the severity of pain, narcotic analgesics are almost always used during the attacks (36). Due to the repeated infarctions and subsequent fibrosis, the spleen is usually too small in adults. Eventually, a functional and anatomic asplenism develops due to the decreased antibody production, prevented opsonization, and reticuloendothelial dysfunction. Terminal consequence of the asplenism is an increased risk of infections with Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis-like encapsulated bacteria. Particularly, pneumococcal infections are so common in early childhood with higher mortality rates. The causes of death were infections in 56% of infants in a previous study (34). In another study, the peak incidence of death among children occured between 1 and 3 years of age, and the deaths under the age of 20 years were predominantly caused by pneumococcal sepsis (37). Adult patients, even those who appear relatively fit, are susceptible to sepsis, multiorgan failures, and sudden death during acute painful crises due to the severe immunosuppression in them (38, 39). SCD can affect all vascular organ systems of the body (40, 41). 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. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature (12). Delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies may decrease the expected survival time further (42). Actually, RBC supports must be given immediately during all medical or surgical procedures in which there is an evidence of clinical deterioration (43). 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 suppressed in patients with the SCD ($p<0.000$ for both) in the present study. On the other hand, as an opposite finding to some other reports (44, 45), the body heights were similar in patients with the SCD and control cases,. Probably due to the significantly suppressed 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 (46, 47). On the other hand, the non-suppressed mean ALT value in the SCD patients may indicate hepatic involvement in them (48).

As a conclusion, BMI may be the major determining factor of systolic and diastolic BP in the human body.

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