A much higher prevalence of chronic obstructive pulmonary disease in males with sickle cell diseases even in the absence of smoking and alcohol

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ABSTRACT

Background: We tried to understand prevalence of chronic obstructive pulmonary disease (COPD) in both genders in sickle cell diseases (SCD).

Methods: All cases with the SCD in the absence of smoking and alcohol were included.

Results: The study included 368 patients (168 males). Mean ages were similar in males and females (29.4 versus 30.2 years, respectively, p>0.05). Mean values of body mass index (BMI) were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, p>0.05). Interestingly, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, p=0.002), COPD (20.8% versus 6.0%, p<0.001), and digital clubbing (13.0% versus 5.5%, p<0.001) were all higher in males. Whereas painful crises per year (5.0 versus 5.0), pulmonary hypertension (10.1% versus 12.5%), acute chest syndrome (2.3% versus 3.5%), mortality (8.3% versus 6.5%), and mean age of mortality (29.0 versus 32.5 years) were similar in males and females, respectively (p>0.05 for all).

Conclusion: SCD are severe inflammatory processes on vascular endothelium particularly at the capillary level, since capillary system is the main distributor of hardened RBC into tissues. The capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the underlying cause of COPD in the SCD. Although the similar BMI and absence of smoking and alcohol, the much higher prevalence of COPD may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process in whole body.

Key words: Sickle cell diseases, chronic obstructive pulmonary disease, male sex, chronic endothelial damage, atherosclerosis, metabolic syndrome, aging

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. 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 become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the systemic atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, prolonged infections such as tuberculosis, and chronic inflammatory processes including sickle cell diseases (SCD), rheumatologic disorders, and cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level terminating with an accelerated atherosclerosis induced end-organ failure in early years of life. We tried to understand prevalence of COPD in both genders in the SCD.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD in the absence of smoking and alcohol were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of the patients including painful crises per year and transfused units of red blood cells (RBC) in their lives were learnt. Due to the cumulative atherosclerotic effects of smoking and alcohol together with the SCD, current and/or previous smokers or drinkers at least for a period of one year were excluded from the study. 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 the verbal expressions. Weight in kilogram is divided by height in meter squared (5). 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 serum iron, iron binding capacity, ferritin, total bilirubin, a posterior-anterior chest x-ray film, and a Doppler echocardiogram to measure systolic BP of pulmonary artery were performed. Systolic BP of the pulmonary artery which is 40 mmHg or higher is accepted as PHT (6). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (8). Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). Eventually, the mean age, associated thalassemia minors, BMI, painful crises per year, total bilirubin value of the plasma, transfused units of RBC in their lives, COPD, digital clubbing, PHT, ACS, overall mortality, and mean age of mortality were detected in both genders, 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 368 patients with the SCD (168 males and 200 females). Smoking and alcohol restrictions were the cause of female predominancy in the study cases since both of them are much higher in males. Mean ages of the patients were similar in males and females (29.4 versus 30.2 years, respectively, $p>0.05$). Prevalence of associated thalassemia minor was also similar in both genders (72.0% versus 69.0%, respectively, $p>0.05$). Mean values of BMI were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, $p>0.05$) (Table 1). Interestingly, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, $p=0.011$), transfused units of RBC in their lives (46.8 versus 29.2, $p=0.002$), COPD (20.8% versus 6.0%, $p<0.001$), and digital clubbing (13.0% versus 5.5%, $p<0.001$) were all higher in males, significantly. On the other hand, painful crises per year (5.0 versus 5.0, $p>0.05$), PHT (10.1% versus 12.5%, $p>0.05$), and ACS (2.3% versus 3.5%, $p>0.05$) were similar in both genders. Although the overall mortality during the ten-year follow up period was higher in males (8.3% versus 6.5%, $p>0.05$), the difference was nonsignificant probably due to the small sample size of the mortality cases. Similarly, although the mean age of mortality was lower in males, the difference was nonsignificant (29.0 versus 32.5 years, $p>0.05$), probably due to the small sample size of the mortality cases again (Table 2).

Table 1: Characteristics of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	45.6% (168)		54.3% (200)
Mean age (year)	29.4 ± 9.9 (5-58)	Ns†	30.2 ± 9.9 (8-59)
Associated thalassemia minors	72.0% (121)	Ns	69.0% (138)
BMI‡ (kg/m²)	21.7 ± 3.5 (14.3-32.5)	Ns	21.6 ± 3.7 (14.5-46.4)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index

Table 2: Gender differences in associated pathologies of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.0 (0-36)	Ns†	5.0 ± 8.7 (0-52)
Total bilirubin (mg/dL)	*5.2 ± 4.9 (0.6-29.0)*	*0.011*	*4.0 ± 3.4 (0.6-22.9)*
Transfused units of RBC‡	*46.8 ± 61.0 (0-434)*	*0.002*	*29.2 ± 36.5 (0-206)*
COPD§	*20.8% (35)*	*<0.001*	*6.0% (12)*
Digital clubbing	*13.0% (22)*	*<0.001*	*5.5% (11)*
PHT¶	10.1% (17)	Ns	12.5% (25)
ACS**	2.3% (4)	Ns	3.5% (7)
Mortality	8.3% (14)	Ns	6.5% (13)
Mean age of mortality (year)	29.0 ± 6.9 (19-42)	Ns	32.5 ± 9.0 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Pulmonary hypertension **Acute chest syndrome

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (11, 12). Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped bodies of RBC. Probably loss of elasticity instead of shape is the major pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan but it is exaggerated with inflammations, infections, and various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (13, 14). The SCD may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (16), whereas they were 29.0 versus 32.5 years 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 Turkey (17). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (8). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, and edema all over the body.

COPD is the third leading cause of death with various causes in the world (18). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes of COPD. Regular alcohol consumption may also be important in the inflammatory process of COPD. For example, COPD was one of the most frequent diagnoses in patients with alcohol dependence (19). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (20). Probably an accelerated atherosclerotic process is the major structural background of

functional changes seen in the COPD. The inflammatory process on vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (21, 22). For example, there may be close relationships between COPD, CHD, PAD, and stroke (23). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (24). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (24). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (25). Similarly, COPD may just be one of the terminal endpoints including priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD (26).

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (27). Its atherosclerotic effects are the most obvious in the Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels, and it has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products by means of the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Although its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (28). There may be an increased energy expenditure during smoking (29), and nicotine may decrease caloric intake in a dose-related manner (30). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (31). BMI seems to be the highest in former, the lowest in current, and medium in never smokers (32). Similarly, smoking may also show the weakness of volition to control eating, and prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (33). On the other hand, smoking-induced endothelial damage may increase plasma triglycerides (34), since triglycerides may behave as acute phase reactants whose plasma values may not be negatively affected by pathologic weight loss (35, 36). Additionally, although CHD were detected with similar prevalences in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females (27). Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we thought of some antidepressant properties of smoking and alcohol, the higher prevalences of them may also show some additional stresses on the male sex in life and a shorthened survival.

Probably alcohol consumption also causes a vascular endothelial inflammation all over the body (37). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages that damage organs via oxidative stresses, and these effects lie far beyond lungs and liver. Against the harmful effects of the ROS, there are various enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase, and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (38). Both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats (38), and tobacco smoke had the strongest effect on protein nitrozylation in the brain (38). Ethyl alcohol affected glutathione levels in serum, kidney, and brain and superoxide dismutase activity in the brain (38). Vascular endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was higher among aborigines with alcohol dependence (39). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats (40). Probably, cirrhosis also shows a capillary endothelial inflammation terminating with disseminated hepatic destruction, and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells were proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue in cirrhosis (41). Although the atherosclerotic effect of alcohol is the most obviously seen in the liver due to the highest concentrations of its products via the portal blood flow there (37), alcohol may even cause COPD, clubbing, CRD, PAD, CHD, stroke, and cancers-like other atherosclerotic endpoints by the transport of its products in the blood.

Digital clubbing is characterized by increase of the normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (42). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (43). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (10). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, renal, or hepatic disorders those are characterized by chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD and its prevalence was 10.8% in the previous study (44). It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males in the present study (13.0% versus 5.5%, $p<0.001$) may also show some additional role of male sex on clubbing.

PHT may also be found among atherosclerotic endpoints of the SCD. PHT is defined as the increased BP in the pulmonary artery, vein, or capillaries. It is observed in 60% of systemic sclerosis, 40% of the SCD, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal hypertension, and 0.5% of HIV patients (45). Whereas we detected PHT just in 11.4% (42 cases) of the SCD patients in the present study. Younger mean ages of our study cases (29.4 and 30.2 years of males and females, respectively) may be the cause of the lower prevalence. PHT and COPD may actually have similar atherosclerotic background but PHT may be a more advanced disease since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2% versus 16.3%), and it is nearly equally seen in both genders than the COPD (52.8% versus 78.8% in males) (44). On the other hand, venous PHT is the most commonly seen type in society (46). In venous PHT, left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions. In chronic thromboembolic PHT, blood vessels are blocked or narrowed with clots that lead to a similar pathophysiology with arterial PHT (47). In hypoxic PHT, hypoxia is thought to cause vasoconstriction or tightening of pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCD due to the inflammated and edematous capillary endothelium secondary to the damage of abnormally hardened RBC in the lungs (48). Whatever the initial cause, PHT involves vasoconstriction or tightening of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of heart causes thickening and enlargement of right ventricle, right heart failure, and cor pulmonale. As blood flowing through lungs decreases, left heart receives less blood. This blood may also carry less oxygen than normal in the SCD due to the capillary endothelial inflammation and edema. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activity

ACS is responsible for considerable mortality in the SCDs (49). It usually occurs as a single episode, and a past history of an ACS is associated with an early mortality. It is usually seen between the ages of 2 to 4 years, and the risk decreases with age (50). The decreased incidence with age may be due to the excess mortality of the ACS and fewer viral and bacterial episodes in the older age groups due to acquired immunities. The incidence of ACS is more common in sickle cell anemia (Hb SS) cases, and a higher white blood cells (WBC) count is associated with a higher incidence (49, 50). Probably ACS is a sudden onset event without a chronic inflammatory background in the SCD (51). It has a complex nature, and one of the major clinical problems lies in distinguishing between infections, infarctions, and fat embolism in the ACS. For example, ACS did not show an infectious etiology in 66% of episodes (49, 50). Similarly, 12 of 27 episodes of ACS had evidence of fat embolism as the cause (52). But according to our experiences, the increased basal metabolic rate during systemic infections may terminate with the ACS, and the ACS may be characterized by disseminated endothelial damage, fat embolism, and infarctions at the capillary level all over the lungs. A preliminary result from the Multi-Institutional Study of Hydroxyurea indicated a significant reduction of ACS with hydroxyurea in the SCD (53). Hydroxyurea interferes with cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase (54). The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyper-proliferating cells. The main action of hydroxyurea is the suppression of leukocytosis and thrombocytosis via blocking the DNA synthesis in the SCD (54). In this way, the continuous inflammatory process of the SCD that initiated at birth on the vascular endothelium is suppressed to some extent. Due to the same action, hydroxyurea is also used in moderate and severe psoriasis to suppress hyper-proliferating skin cells. Similar to the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of the destructive process is probably exaggerated by the patients' own immune system, particularly by the actions of WBC and platelets (PLT). So suppression of excessive proliferation of WBC and PLT probably limits the endothelial damage-induced tissue ischemia and infarctions all over the body. Some authors suggested that antibiotics do not shorten the clinical course (8, 55), and RBC transfusions must be given whenever there is evidence of clinical deterioration in the ACS (56). RBC transfusions decrease sickle cell concentration in the circulation and suppress the bone marrow production of abnormal RBC. In this way, they prevent further sickling-induced damage to the lungs or other organs. RBC transfusions should be performed early in the course since they have prophylactic benefit rather than late, when the patient is clearly comatose. According to our ten-year experiences on the SCD, simple and repeated RBC transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions at each time rather than preparation of six units or more provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusions of one or two units of RBC suspensions at each time decreases the severity of pain, and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions at each time by means of simple transfusions will decrease transfusion-related complications including infections, iron overload, and cross-matching problems in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange.

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the tissues. The capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of COPD in the SCD. Despite the similar BMI and absence of smoking and alcohol, the much higher prevalence of COPD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

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