Pulmonary hypertension may not have an atherosclerotic background in sickle cell diseases

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ABSTRACT

Background: **We tried to understand the underlying mechanism of pulmonary hypertension (PHT) in the sickle cell diseases (SCD).**

Methods: **All patients with the SCD were included.**

Results: **The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%, p<0.001) and alcohol (4.9% versus 0.4%, p<0.001) were higher in males, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000), disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher but not PHT (12.6% versus 11.7%, p>0.05) in males, significantly.**

Conclusion: **SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking, alcohol, and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like atherosclerotic consequences in male sex, PHT was not higher in them in the present study. In another definition, PHT may not have an atherosclerotic background in the SCD. Instead, the hardened RBC-induced capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the major underlying cause.**

Key words: **Sickle cell diseases, chronic endothelial damage, pulmonary hypertension, atherosclerosis, male sex, smoking, alcohol**

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing persistent 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. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, arterial walls become thickened, their lumens are narrowed, and they lose their elastic nature, which reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are male sex, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory and infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers, for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), 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 (1-3). Although early withdrawal of the causative factors may delay terminal consequences, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, or stroke due to their fibrotic nature (4, 5). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures in early years of life. We tried to understand the underlying mechanism of pulmonary hypertension (PHT) 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 were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBC) in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, priapism, and symptoms of benign prostatic hyperplasia (BPH) including urgency, weak stream, incomplete emptying, and nocturia were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. 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, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus (HIV), a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (6). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minors show a milder clinic than the sickle cell anemia (SCA) alone (7). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (8). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (9). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (10). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. 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 (11, 12). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, the mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, and consequences of the SCD were detected in both genders, and compared in between. Additionally, mean ages of the consequences were calculated. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCD (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, $p>0.05$). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, respectively, $p>0.05$). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly ($p<0.001$ for both) (Table 1).

Similarly, transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), disseminated teeth loss (<20 teeth present) (5.4% versus 1.4%, $p<0.001$), COPD (25.2% versus 7.0%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%,

p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), CHD (18.0% versus 13.2%, p<0.05), CRD (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in male sex, significantly. There were 11 males (4.9%) with symptoms of BPH with a mean age of 41.5 ± 10.6 (27-58) years. Additionally, there were 23 males (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 ± 8.4 (19-50) in males and 33.3 ± 9.2 (19-47) years in females (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the consequences, PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may indicate advanced diseases in such patients due to the significantly shortened survival of the SCD in both genders (Table 3).

Table 1: Characteristic features of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	*<0.001*	***6.1% (13)***
Alcoholism	***4.9% (11)***	*<0.001*	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	*0.000*	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	*<0.001*	***1.4% (3)***
COPD§	***25.2% (56)***	*<0.001*	***7.0% (15)***
Ileus	***7.2% (16)***	*<0.001*	***1.4% (3)***
Cirrhosis	***8.1% (18)***	*<0.001*	***1.8% (4)***
Leg ulcers	***19.8% (44)***	*<0.001*	***7.0% (15)***
Digital clubbing	***14.8% (33)***	*<0.001*	***6.6% (14)***
CHD¶	***18.0% (40)***	*<0.05*	***13.2% (28)***
*CRD***	***9.9% (22)***	*<0.05*	***6.1% (13)***
Stroke	***12.1% (27)***	*<0.05*	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
Acute chest syndrome	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease
**Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
Acute chest syndrome	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD*	33.6 ± 9.2 (13-58)
PHT†	*34.0 ± 10.0 (18-56)*
Leg ulcers	*35.3 ± 8.8 (17-58)*
Digital clubbing	*35.4 ± 10.7 (18-56)*
CHD‡	*35.7 ± 10.8 (17-59)*
DVT§ and/or varices and/or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
CRD¶	*39.4 ± 9.7 (19-59)*
*BPH***	*41.5 ± 10.6 (27-58)*

*Chronic obstructive pulmonary disease †Pulmonary hypertension ‡Coronary heart disease §Deep venous thrombosis ¶Chronic renal disease **Benign prostatic hyperplasia

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (13, 14). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of RBC. Probably loss of elasticity instead of shape is the main 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 exaggerated with inflammation, infection, or 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 (15, 16). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (17), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, the mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (18), whereas they were 30.2 and 33.3 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 (19). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (10). 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, edema, and tissue hypoxia all over the body.

PHT is found among the terminal consequences of the SCD (20). PHT is defined as the increased BP in pulmonary artery, vein, or capillaries. It is seen in 60% of systemic sclerosis, 40% of the SCD, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal HT, and 0.5% of HIV patients (21). Whereas we detected PHT just in 12.2% of the SCD patients in the present study. The relatively younger mean ages of our patients (30.8 years of males versus 30.3 years of females) may be a cause of the lower prevalence. Although the highly atherosclerotic background of the COPD, PHT may actually have a different underlying mechanism in the SCD since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2% versus 16.3%), and it is equally seen in both genders than the COPD (52.8% versus 78.8% in males) in the present study. Additionally, although the higher prevalences of smoking, alcohol, and disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like other atherosclerotic consequences in male sex, the prevalence

of PHT was not higher in males with the SCD, significantly (12.6% versus 11.7%, respectively, p>0.05). On the other hand, venous PHT is the most common cause of PHT in the society (22). In venous PHT, left heart fails to pump blood efficiently, leading to the 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, which leads to a similar pathophysiology with arterial PHT (23). In hypoxic PHT, hypoxia is thought to cause vasoconstriction of the pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCD due to the inflammated and edematous capillary endothelium around the alveoli secondary to the damage of abnormally hardened RBC (24). Whatever the initial cause, PHT involves vasoconstriction of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of the heart causes thickening and enlargement of the 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 as in the SCD due to the capillary endothelial inflammation and edema around the alveoli. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activity. Although the possible arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the main cause of PHT in the SCD since the capillary system is the main distributor of the abnormally hardened RBC into the lungs.

COPD is the third leading cause of death with various causes and pathophysiologic mechanisms in the world (25). It is an inflammatory disease that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes. As also observed in the present study, regular alcohol consumption may also be important in the inflammatory process. For example, COPD was one of the most common diagnoses in patients with alcohol dependence (26). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (27). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of 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 (28, 29). For example, there may be close relationships between COPD, CHD, PAD, and stroke (30). 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 (31). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (31). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD cases (32). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalences of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD patients with COPD (33).

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 (34). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (35). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (12). But according to our experiences, digital clubbing is frequently associated with smoking alone and with pulmonary, cardiac, renal, or hepatic disorders that are characterized with chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs that 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 present study. 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 digital clubbing in males (14.8% versus 6.6%, p<0.001) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (36), and the ratio was 13.5% in the present study. Its incidence increases with age, male sex, and SCA (37). Similarly, its ratio was higher in males (19.8% versus 7.0%, p<0.001), and mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (36). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (36). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major underlying cause in the SCD (37). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are much more common in males. Hydroxyurea is the only drug that was approved by Food and Drug Administration for the treatment of SCD (17). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (19). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (38). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patient's own immune system. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (39). According to our ten-year experience, prolonged resolution of leg ulcers with

hydroxyurea therapy may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged endothelial damage, inflammation, and edema at the capillary level in the SCD.

Both frequency and complications of cirrhosis are increasing in the world, and it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (5). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even at childhood at the moment (40). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (40). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (41). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (42). NAFLD may be considered as the hepatic consequences of the metabolic syndrome and SCD (13, 43). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (44). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (45). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (45, 46). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among the atherosclerotic consequences of the metabolic syndrome and SCD.

Both frequency and complications of CRD are increasing all over the world, too (47). The increased frequency and complications of CRD may be explained by aging of the societies and increased prevalence of excess weight all over the world, since CRD may also be found among the atherosclerotic consequences of the metabolic syndrome (48). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory and infectious processes may be the major underlying causes of the endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arteriols. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, and tissue hypoxia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses during acceleration of tissue inflammation and immune cell activation (49). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (48). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (50). Excess weight also causes renal vasodilation and glomerular hyperfiltration that initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (50). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (51). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (50). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (52). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (52), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory and infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (45). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (53). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure again (54). In another definition, CRD may also be found among the atherosclerotic consequences of the metabolic syndrome and SCD, again (55).

Stroke is an important cause of death, and thromboembolism in the background of atherosclerosis is the most common cause of it. Aging, male sex, smoking, increased serum glucose and lipids, elevated arterial BP, and excess weight may be the major accelerator factors of it. Stroke is also a common complication of the SCD (56, 57). Similar to the leg ulcers, stroke is higher in SCA cases (58). Additionally, a higher WBC count is associated with a greater incidence of stroke (38). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (59). Probably, stroke is a complex and terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation induced endothelial edema may be much more important. Infections and other stressful conditions may precipitate stroke, since increased metabolic rate during such episodes may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary inflammation and edema (60).

Although the presence of an accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (61). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include aging, obesity, menopause, pregnancy, and heredity. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination must be performed in upright position. Although the relatively younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively) and significantly lower body mass index of the SCD cases in the literature (16), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCD (61). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (62). It is an emergency since damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (62). It is seen with hematological and neurologic disorders including SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (63, 64). Ischemic (veno-occlusive and low flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial and high flow) are the three types of priapism (65). Ninety-five percent of clinically presented priapisms are the ischemic or low-flow disorders in which blood cannot return adequately from the penis into the body as in the SCD, and they are very painful (62, 65). The other 5% are nonischemic high-flow type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system of the penis (62). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (62). RBC support is the treatment of choice in acute phase in the SCD (66). Whereas in the chronic phase, hydroxyurea should be the treatment of choice of the priapism in the SCD. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

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 hardened RBC into the tissues. Although the higher smoking, alcohol, and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like atherosclerotic consequences in male sex, PHT was not higher in them in the present study. In another definition, PHT may not have an atherosclerotic background in the SCD. Instead, the hardened RBC-induced capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the major underlying cause.

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