Pathophysiology of pulmonary hypertension in sickle cell diseases

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ABSTRACT

Background: **Pulmonary hypertension (PHT) is common in sickle cell diseases (SCDs).**

Methods: **All patients with SCDs 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%) and alcohol (4.9% versus 0.4%) were higher in males (p<0.001 for both). Disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), transfused units of red blood cell (RBC) (48.1 versus 28.5, p=0.000), 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 also higher in males. There were 31 mortality cases (17 males) with similar mean ages in males and females (30.2 versus 33.3 years, respectively, p>0.05). Mean ages of COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), deep venous thrombosis and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and benign prostatic hyperplasia (41.5 years) were higher.**

Conclusion: **SCDs are severe inflammatory processes on vascular endothelium particularly at capillary level, since the capillary system is the main distributor of hardened RBCs into tissues. Although various arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of PHT in SCDs.**

Key words: **Sickle cell diseases, chronic endothelial damage, atherosclerosis, pulmonary hypertension**

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Introduction

Chronic endothelial damage may be the leading cause of aging and associated morbidity and mortalities 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. Therefore 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 and thus reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, 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, SCDs are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failure in early years of life. We tried to understand the pathophysiology of PHT in the SCDs.

Materials 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 SCDs were included into the study. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, epilepsy, deep venous thrombosis (DVT), transfused units of red blood cell (RBC) in their lives, surgical operations, leg ulcers, stroke, priapism, and benign prostatic hyperplasia (BPH) symptoms including urgency, weak stream, incomplete emptying, and nocturia were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, 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. Patients with disseminated teeth loss (<20 teeth present) were detected. Cases with acute painful crises 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 (5). Associated thalassemia minor was detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (6). 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 is diagnosed clinically with the presence of new infiltrates on chest X-ray film, fever, cough, sputum production, dyspnea, or hypoxia (8). 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 (9, 10). 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 also diagnosed with the echocardiographic findings. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, thalassemia minor, smoking, alcohol, painful crises per year, and accelerated atherosclerotic endpoints of the SCDs were detected in both genders, and compared in between. Beside that, mean ages of these atherosclerotic endpoints were detected in them. 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 SCDs (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 significantly higher in males ($p<0.001$ for both) (Table 1). Disseminated teeth loss (<20 teeth present) (5.4% versus 1.4%, $p<0.001$), transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), 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%,

Table 1: Characteristic features of the study cases

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
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 according to the gender distribution

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Disseminated teeth loss (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
Transfused RBC‡ units	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
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)
Respiratory sinus arrhythmia	4.9% (11)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)

*Sickle cell diseases

†Nonsignificant (p>0.05)

‡Red blood cell

§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 ages of the patients
Respiratory sinus arrhythmia	27.2 ± 8.3 (18-50)
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 loss (<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

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 males, significantly. There were 11 males (4.9%) with BPH symptoms with a mean age of 41.5 ± 10.6 (27-58) years. All of the BPH patients could be treated with once daily 4 milligrams of doxazosin, orally. 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 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 2). When we evaluated the mean ages of the consequences of the SCDs, COPD (33.6 years), 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 be the alarming consequences indicating an advanced disease in such patients due to the significantly shortened survival of the SCDs in both genders (Table 3).

Discussion

SCDs 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 structures of RBCs. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCDs 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, infection, or various stresses of the body. The abnormally hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (13, 14). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the abnormally hardened RBCs 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, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (16), 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 the Antakya region of 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 SCDs (8). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. 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 and pathophysiologic mechanisms in the world (18). 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 (19). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (20). 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 (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). As a result, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCDs patients associated with COPD (26).

PHT may also be found among one of the atherosclerotic terminal endpoints of the SCDs. PHT is defined as the increased BP in pulmonary artery, vein, or capillaries. It is seen in 60% of systemic sclerosis, 40% of SCDs, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal HT, and 0.5% of HIV patients (27). Whereas we detected PHT just in 12.2% (53 cases) of the SCDs patients in the present study. Younger mean ages of our study cases (30.8 years of males versus 30.3 years of females) may be the cause of the lower prevalence. PHT and COPD may actually have similar atherosclerotic underlying mechanisms during the development 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 (52.8 versus 78.8% in males) than the COPD in the present study. On the other hand, venous PHT is the most common cause of PHT in the society (28). 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, which leads to a similar pathophysiology with arterial PHT (29). 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 SCDs due to the inflammated and edematous capillary endothelium, secondary to the damage of abnormally hardened RBCs in the lungs (30). 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 as in the SCDs 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. Although various arterial and venous involvement mechanisms, capillary endothelial involvement may be the major underlying cause of PHT in the SCDs since the capillary system is the main distributor of the abnormally hardened RBCs into the lungs.

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 (31). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (32). 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 alone and with pulmonary, cardiac, renal, or hepatic disorders which are characterized with chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs and those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCDs 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 SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males ($p<0.001$) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (33), and the ratio was 13.5% in the present study. Its incidence increases with age, male sex, and HbSS genotype (34). 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 (33). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (33). The abnormally hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary

level may be the major underlying cause in the SCDs (34). 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 SCDs. The hardened RBCs 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, pooling of blood probably delays 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 the Food and Drug Administration for the treatment of SCDs (15). 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 (17). Its main action may be the suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs (35). Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. 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 (36). According to our ten-year experiences, 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, edema, and fibrosis at the capillary level in the SCDs.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are much more common in females and metabolic syndrome. Normally, leg muscles pump veins to return blood against 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 the 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 SCDs cases in the literature (14), DVT and/or varices and/or telangiectasias of the lower limbs were higher among the study patients (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement of the SCDs.

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 (4). 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, non-alcoholic 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 in childhood at the moment (37). 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 (37). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (38). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (39). NAFLD may be considered as the hepatic consequences of the metabolic syndrome and SCDs (11, 40). 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 (41). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effect of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (42). 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 (42, 43). As a result, beside COPD, PHT, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among one of the atherosclerotic terminal endpoints of the metabolic syndrome and SCDs.

Both frequency and complications of CRD are increasing all over the world, too (44). 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 one of the terminal atherosclerotic endpoints of the metabolic syndrome (45). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or 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 arterioles. 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, tissue hypoxia, and tissue 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 (46). 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 CIMT (45). 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 (47). 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 (47). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (48). With prolonged weight excess, there are increased urinary protein excretion, lost nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (47). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (49). The inflammatory and eventual 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 (49), 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 or infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (42). 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 (50). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure (51). In another definition, CRD may also be found among one of the atherosclerotic terminal endpoints of the metabolic syndrome and SCDs (52).

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of hardened RBCs into tissues. Although various arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of PHT in the SCDs.

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