AVASCULAR NECROSIS MAY NOT HAVE AN ATHEROSCLEROTIC BACKGROUND IN SICKLE CELL DISEASES

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Received: June 2021; Accepted: July 2021; Published: August, 2021
Citation: Mehmet Rami Helvaci et al. Avascular necrosis may not have an atherosclerotic background in sickle cell diseases. Middle East Journal of Nursing 2021; 15(3): 13-23.DOI: 10.5742/MEJN2021.9378011

Abstract

Background: We tried to understand whether or not there is a significant association between avascular necrosis (AVN) and atherosclerosis in 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 male and female genders (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 male gender, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000) were also higher in male gender, significantly. Similarly, 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 in male gender but not AVN (24.3% versus 25.4%, p>0.05), 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 and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, AVN was not higher in them, significantly. In another definition, AVN may not have an atherosclerotic background in the SCD.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, avascular necrosis, male gender, smoking, alcohol

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing persistent tissue hypoxia in 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, 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 atherosclerotic process are male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or 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, stroke, benign prostatic hyperplasia (BPH), 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 can not be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, stroke, or BPH 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 atherosclerotic process induced end-organ failures in early years of life (6). We tried to understand whether or not there is a significant association between avascular necrosis (AVN) and atherosclerosis 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 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, 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 AVN was diagnosed via MRI (7). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD patients with associated thalassemia minors show a milder clinic than the sickle cell anemia (SCA) alone (8). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (PHT) (9). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (10). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest X-ray film, fever, cough, sputum production, dyspnea, or hypoxia (11). 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 male and 1.2 mg/dL or higher in female genders. 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 (12, 13). An exercise electrocardiogram is performed in patients with an abnormal electrocardiogram 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). The mean ages of the patients were similar in male and female genders (30.8 versus 30.3 years, respectively, p>0.05). Prevalence of associated thalassemia minor 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 much higher in male gender, significantly (p<0.001 for both) (Table 1). Interestingly, transfused units of RBC in their lives (48.1 versus 28.5, p=0.000) were also much higher in male gender, significantly. Similarly, disseminated teeth losses (<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 gender but not AVN (24.3% versus 25.4%, p>0.05), significantly. There were 11 patients (4.9%) with the symptoms of BPH with a mean age of 41.5 (27-58) years. Additionally, there were 23 patients (10.3%) with priapism with a mean age of 33.4 (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 (19-50) in male and 33.3 (19-47) years in female genders (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the consequences, stroke (33.5 years), COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT or varices 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 patients

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 patients

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**** or varices or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
AVN*****	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

*****Avascular necrosis

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)
AVN*	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¶ or varices 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)*

*Avascular necrosis †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 (14, 15). 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 minor, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated during 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 (16, 17). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBC into the tissues (18). 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 male and female genders in the literature, respectively (19), 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 (20). Actually, RBC supports must be given immediately during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD (11). 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.

Bone involvement is the most common clinical manifestation of the SCD both in the acute events including painful crises and in the chronic events including AVN, osteomyelitis, and septic arthritis (21, 22). For example, we detected AVN in 24.8% of the SCD patients in the present study. AVN is one of the most devastating musculoskeletal manifestations of the SCD (23). AVN or osteonecrosis or bone infarction or aseptic necrosis or ischemic bone necrosis is a disease where there is cellular death of bone components due to interruption of the blood supply. Without blood, the bone tissue dies and the bone collapses. If the AVN involves the bones of a joint, it often leads to destruction of the articular surface that is called osteochondritis dissecans. SCD, decompression sickness, vascular compression, and vasculitis including rheumatoid arthritis and systemic lupus erythematosus

are the common causes of the AVN. Experimental evidence suggests that the bone cells (osteocytes, osteoclasts, osteoblasts, etc.) die within 12-48 hours, and the fat cells of the bone marrow die within 5 days after reduction of the blood supply. After reperfusion, repair of ischemic bone occurs in two phases. First, there is angiogenesis and migration of undifferentiated mesenchymal cells from the adjacent living bone tissue into the dead marrow spaces, as well as entry of macrophages that degrade dead cellular and fat debris. Second, there is cellular differentiation of mesenchymal cells into osteoblasts or fibroblasts. Normally, bone is broken down and rebuilt up, continuously. Whereas in the AVN, the healing process is usually ineffective and the bone tissue is broken down faster than the body can rebuild it up again. Thus some clinicians also prescribe biphosphonates to reduce the osteoclastic activity in the early phases of the AVN. If the process is left untreated, the bone collapses, and the articular surface is broken down, leading to pain and arthritis. In the earlier stages of the disease (stage I and II of the Ficat and Arlet classification), the articular surface is preserved, and X-ray images are normal (24, 25). Therefore MRI is the chief method both for the diagnosis and staging of AVN, and should be performed in unexplained bone pain in young patients with normal X-rays. In the more advanced stages (stage III and IV), the articular surface collapses (25). AVN can affect any bone in the body, and half of the cases show multiple sites of involvement in the SCD. Clinical AVN most commonly affects the ends (epiphysis) of long bones. It primarily affects the femoral head in more than 75% of cases, followed by the humeral head, knee, and small bones of the wrist and foot (25, 26). Although the exact pathophysiology is unknown, an acute-onset capillary endothelial damage, inflammation, and edema caused by the hardened RBC around the bone tissues may be the major underlying cause in the SCD. Since although the higher prevalences of smoking and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender in the SCD, the prevalence of AVN was not higher in them, significantly (24.3% versus 25.4%, respectively, $p>0.05$). On the other hand, AVN frequently affects young patients, and is usually seen between the ages of 30 and 50 years that may also indicate a nonatherosclerotic background of the AVN. Similarly, the mean age of AVN was 32.8 years in the SCD patients in the present study.

COPD is the third leading cause of death with various causes in the world (27). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Although aging, smoking, and excess weight may be the major underlying risk factors, regular alcohol consumption may also be important in the inflammatory process. For example, COPD was one of the most common diagnoses in alcohol dependence (28). Furthermore, 30-day readmission rates were higher in COPD with alcoholism (29). Probably an accelerated atherosclerotic process is the main structural background of functional changes of the COPD. The inflammatory process on the vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and 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 (30, 31). For example, there may be close relationships between COPD, CHD, PAD, and stroke (32). Furthermore, two-thirds of mortality 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 (33). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (33). In another study, 27% of mortality was due to the cardiovascular diseases in the moderate and severe COPD (34). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD patients with COPD (35).

Digital clubbing is characterized by an increased normal angle of 165° between the nail bed and nail fold, increased convexity of the nail fold, and thickening of the whole distal finger (36). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (37). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (13). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, and hepatic disorders and smoking which are characterized by chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each others' functions in a short period of time. On the other hand, digital clubbing is also common in 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 effects of the SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in male gender (14.8% versus 6.6%, $p<0.001$) may also indicate some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (38), and the ratio was 13.5% in the present study. The prevalence increases with age, male gender, and SCA (39). Similarly, the prevalence was higher in male gender (19.8% versus 7.0%, $p<0.001$), and the 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. These results may indicate some effects of systemic atherosclerotic process on leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (38). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (38). 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 (39). Prolonged exposure to the hardened cells due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened cells induced venous insufficiencies may also accelerate the process by pooling of causative RBC in the legs, and vice versa. Similarly, pooling of blood may also have some effects on higher prevalences of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, the pooling may be the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened RBC, the higher prevalences of smoking and alcohol may also have some additional effects on the leg ulcers by accelerating the atherosclerotic process in male gender. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the treatment of SCD (18). 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 (20). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (40). Although the presence of a continuous damage by hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the 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 (41). According to our ten-year experiences, prolonged resolution of leg ulcers in most but not all of the SCD patients with hydroxyurea may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged vascular endothelial inflammation and edema at the capillary level. Probably due to the irreversible fibrotic process on vascular endothelium, the drug is not so effective in terminal patients.

The prevalence of cirrhosis is 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). Despite 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 (42). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (42). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased cardiovascular diseases (43). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (44). NAFLD may be considered as the hepatic consequence of the metabolic syndrome and SCD (14, 45). Smoking may also take a role in the endothelial inflammation in the liver since the inflammatory effects of smoking on vascular endothelium is well-known with Buerger's disease and COPD (46). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with an accelerated atherosclerosis in smokers. Atherosclerotic effects of alcohol are much more prominent on 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 (47). For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (47). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be one of the atherosclerotic consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (48). The increased prevalence of CRD may be explained by aging of the societies and increased prevalence of excess weight since CRD may also be one of the atherosclerotic consequences of the metabolic syndrome (49). Aging, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major causes of the vascular endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly endothelial cells of the renal arteriols. Due to the prolonged irritations of the vascular endothelium, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, renal hypoxia and infarcts, and fibrosis. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses by means of acceleration of tissue inflammation and immune cell activation (50). For instance, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) showed significant correlations with the CIMT (49). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to activations of sympathetic nervous and renin-angiotensin systems, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (51). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (51). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys by causing chronic endothelial damage in long term (52). With prolonged excess weight, 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 more rapidly (51). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in CRD (53). 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 CRD (53), 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 an accelerated atherosclerosis on renal vascular endothelium (47). Although CRD is mainly thought to be an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome and SCD including CHD, COPD, PAD, cirrhosis, and stroke (54). For example, the most common cause of death was the cardiovascular diseases in the CRD again (55). In another definition, CRD may also be one of the atherosclerotic consequences of the metabolic syndrome and SCD (56).

Stroke is an important cause of death in human beings, and thromboembolism in the background of atherosclerosis is the most common cause of stroke. Aging, male gender, smoking, alcohol, hyperglycemia, dyslipidemia, elevated BP, excess weight, and chronic inflammatory or infectious processes may be the major triggering factors of the stroke. Stroke is also a frequent complication of the SCD (57, 58). Similar to the leg ulcers, stroke is higher in the SCA cases (59). Additionally, a higher WBC count is associated with a greater incidence of stroke (40). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (60). Probably, stroke is a complex and terminal event, and it may not have a macrovascular origin in the SCD. Instead disseminated capillary endothelial inflammation and edema may be much more important in the process. Associated inflammatory or infectious disorders or stressful conditions of the human body may precipitate stroke in the SCD, since increased metabolic rate during such episodes may accelerate sickling. On the other hand, a significant reduction of stroke with hydroxyurea therapy may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary endothelial inflammation and edema (61).

Although the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (62). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Risk factors include aging, excess weight, menopause, pregnancy, and heredity. 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, DVT or varices or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus the physical examination must be performed in upright position. Although the younger mean ages of the patients in the present study (30.8 and 30.3 years in male and female genders, respectively) and significantly lower mean body mass index of the SCD patients in the literature (17), DVT or varices or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in male and female genders, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCD (62). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (63). 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 (63). It is seen with hematological and neurologic disorders including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (15, 64, 65). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of priapism (66). Ninety-five percent of clinically presented priapisms are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the body as in the SCD, and these cases are very painful (63, 66). 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 (63). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (63). RBC support is the treatment of choice in acute phase in the SCD (67), whereas in chronic phase, hydroxyurea therapy should be the treatment of choice. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of attacks and consequences if iniatiated early, but the success rate is low due to the excessive fibrosis around the capillaries if initiated later.

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 and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, AVN was not higher in them, significantly. In another definition, AVN may not have an atherosclerotic background in the SCD. Instead, an acute-onset capillary endothelial damage, inflammation, and edema caused by the hardened RBC around the bone tissues may be the major cause of AVN in the SCD.

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