Acute chest syndrome may not have an atherosclerotic background in sickle cell diseases

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ABSTRACT

Background: We tried to understand whether or not there is a significant relationship between acute chest syndrome (ACS) and atherosclerosis in sickle cell diseases (SCD).

Methods: All patients with the SCD were included.

Results: The study included 434 patients (222 males) 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 males, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000) were also higher in males, 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 males but not ACS (2.7% versus 3.7%, p>0.05) in the SCD.

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, ACS was not higher in them, significantly. In another definition, ACS may not have an atherosclerotic background in the SCD.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, acute chest syndrome, male gender, smoking, alcohol

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing tissue infarcts 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 vessels 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 irreversible 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, and benign prostatic hyperplasia (BPH) which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although the 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, stroke, or BPH due to their fibrotic natures (4-6). 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 (7). We tried to understand whether or not there is a relationship between acute chest syndrome (ACS) 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 or infectious or traumatic 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 avascular necrosis was diagnosed via MRI (8). Autosplenectomy is diagnosed in the absence of any history of surgical splenectomy, ultrasonographically. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via the HPLC. 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). ACS is diagnosed with the presence of new infiltrates on chest X-ray film, fever, cough, sputum, dyspnea, or hypoxia, clinically (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 the 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, laboratory parameters, and ultrasonographic results. 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 patients. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of 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 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, autosplenectomy, and other consequences of the SCD and mean ages of the consequences were detected in both genders, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCD (222 males and 212 females). Their mean ages were similar in males and females (30.8 versus 30.3 years, respectively, p>0.05). Prevalence of associated thalassemia minors were similar in males and females, 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 males, significantly (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 versus 28.5, p=0.000) were also higher in males, 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 males but not ACS (2.7% versus 3.7%, 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 males and 33.3 (19-47) years in females (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the irreversible 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)
Avascular necrosis	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)
ACS*****	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 *****Acute chest syndrome

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)
ACS*	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	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)*

*Acute chest syndrome †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 an 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 very rare in peripheric blood samples of the SCD with associated thalassemia minors, and overall survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated during inflammation, infection, and various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia and infarcts 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 males and females in the literature (19) whereas they were 30.2 and 33.3 years in the present study, respectively. 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 during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD, immediately (11). RBC supports decrease sickle cell concentration in the circulation, and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, edema, and tissue ischemia and infarcts all over the body.

ACS is responsible for a considerable mortality in the SCD (21). According to the literature, it occurs most often as a single episode, and a past history is associated with a high mortality rate (21). Similarly, all of 14 cases with the ACS had just a single episode, and two of them were fatal in spite of the rigorous RBC and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between the ages of 2 to 4 years, and its incidence decreases with age (22). Similarly, as a difference from other atherosclerotic consequences, incidence of ACS did not show an increase with aging, and mean ages of the ACS and SCD were 30.3 and 30.5 years in the present study, respectively ($p>0.05$). The decreased incidence with aging may be due to the high mortality rate during the first episode, an acquired immunity against various antigens with aging, and decreased strength of immune response by aging, since an exaggerated immune response may be the major cause of death in the ACS. On the other hand, ACS may also show an inborn severity of

the SCD. For example, its incidence is higher in severe cases such as cases with sickle cell anemia (SCA) or cases with higher white blood cells (WBC) counts (21, 22). Probably, ACS is a complex event, and it does not indicate an absolute diagnosis in the majority of cases. The major clinical problem lies in distinguishing between infections, infarctions, and fat embolisms. For example, ACS did not show an infectious etiology in 66% of cases in the above studies (21, 22). Similarly, 12 of 27 cases of ACS had evidence of fat embolisms in another study (23). But according to our ten-year experiences, the increased metabolic rate during serious infections may also terminate with the ACS. In another word, the ACS may be a relative insufficiency of the lungs during the serious metabolic conditions. On the other hand, an exaggerated immune response against various antigens or abnormal RBC may also be important in the high mortality rates of the ACS. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCD indicating a significant reduction of ACS episodes with hydroxyurea therapy suggests that a substantial number of episodes are secondary to the increased numbers of WBC and platelets (PLT) induced vascular endothelial damage (24). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD that may also be a cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, some authors indicated that antibiotics do not shorten the clinical course (25, 26), and RBC support must be given early in the course since it has also prophylactic benefit. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. So they prevent further sickling and the exaggerated immune response induced vascular damage in the lungs and all over the body. According to our observations, simple and repeated transfusions are superior to RBC exchange (27, 28). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or greater provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their surroundings, since RBC transfusions probably have the strongest analgesic effects during the severe painful crises. Actually, the decreased severity of pain may also be one of the most sensitive indicators of the decreased inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications, including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary health centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange which needs trained staff and additional devices.

COPD is the third leading cause of death in the world (29). 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 instance, COPD was one of the most common diagnoses in alcohol dependence (30). Furthermore, 30-day readmission rates were higher in the COPD with alcoholism (31). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The inflammatory process of the vascular endothelium is enhanced by the release of various chemicals by inflammatory cells, and terminates with an advanced atherosclerosis and pulmonary losses. Although 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 (32, 33). For example, there may be close relationships between COPD, CHD, PAD, and stroke (34). 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 (35). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (35). In another study, 27% of mortality were due to the cardiovascular diseases in the moderate and severe COPD (36). 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 with COPD (37).

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 or toes (38). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (39). In the previous study, only 40% of clubbing cases turned out to have significant diseases while 60% remained well over the subsequent years (13). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, or hepatic disorders or smoking which are characterized with 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 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 indicate some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with SCD (40), and the ratio was 13.5% in the present study. The prevalence of leg ulcers increases with age, male gender, and SCA (41). It is shown that SCA showes a more severe clinic than SCD with associated thalassemia minors (42). Similarly, the prevalence was higher in males (19.8% versus 7.0%, $p<0.001$), and the mean age of the patients with leg ulcers was significantly higher than the others in the present study (35.3 versus 29.8 years, $p<0.000$). These results may indicate effects of systemic atherosclerosis on the leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of ulcers relapse in a period of one year (40). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (40). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the main cause in the SCD (41).

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 prevalence of smoking and alcohol may also have some effects on the leg ulcers by accelerating the atherosclerotic process in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the 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 WBC and PLT in the SCD (43). Although the presence of a continuous damage by hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the higher numbers of WBC and PLT. 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 (44). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea in most patients 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 the vascular endothelium, hydroxyurea is not so effective in terminal patients with the leg ulcers.

Cirrhosis is increasing in the world, and is the 11th leading cause of death globally (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 (45). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (45). Beside terminating with cirrhosis, NAFLD is associated with higher cardiovascular diseases and overall mortality rates (46). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (47). NAFLD may be considered as a hepatic consequence of the metabolic syndrome and SCD (14, 48). Smoking may also play 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 (49). 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. For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (50). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may just be one of the consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (51). The increased prevalence of CRD may be explained by aging of the human being and increased prevalence of excess weight, since CRD may also be one of the consequences of the metabolic syndrome (52). Aging, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major underlying 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 an advanced atherosclerosis and subsequent ischemia and infarcts. 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 (53). For instance, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (52). 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 just be some of the mechanisms of the increased BP with excess weight (54). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (54). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys by causing chronic endothelial damage in long term (55). 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 (54). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (56). 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 is not related with the CRD (56), it is not logical, since various metabolites of alcohol circulate even in the renal vasculature, and give harm to the vascular endothelium. Chronic inflammatory or infectious disorders may also terminate with an accelerated atherosclerosis in the kidneys (50). Although the CRD is mainly thought of as an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome and SCD (57). For instance, the most common causes of death were the stroke and CHD in the CRD again (58). In another definition, CRD may just be one of the consequences of the metabolic syndrome and SCD, again (59).

Stroke is an important cause of death in human beings, and thromboembolism on an atherosclerotic background is the most common mechanism of the stroke. Aging, male gender, smoking, alcohol, excess weight and its consequences, and chronic inflammatory or infectious processes may just be some of the triggering factors of the stroke. Stroke is also a frequent complication in the SCD (60, 61). Similar to the leg ulcers, stroke is higher in the SCA cases (62). Additionally, a higher WBC count is associated with a higher risk of stroke (43). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic vascular endothelial inflammation, edema, remodeling, and scarring (63). 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 may precipitate the stroke, since increased metabolic rate during such episodes may accelerate the sickling. On the other hand, 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 endothelial inflammation and edema in the brain (64).

Additional to the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (65). For instance, 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 the 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 males and females, 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 males and females, respectively, $p>0.05$), indicating an additional venous endothelial involvement in the SCD (65). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (66). 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 (66). It is seen with hematological and neurological disorders, including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (15, 67, 68). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of the pathology (69). Ninety-five percent of the clinical cases are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the systemic circulation as in the SCD, and these cases are very painful (66, 69). 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 (66). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (66). RBC support is the treatment of choice in acute phase in the SCD (70). 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 the attacks and consequences if iniatiated early in the course of the disease, 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, ACS was not higher in them, significantly. In another definition, ACS may not have an atherosclerotic background in the SCD.

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