MATHEWS

Review Article

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Sickle Cell Diseases May Show Terminal Consequences of the Metabolic Syndrome in Much Earlier Ages

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ABSTRACT

Background: Sickle cell diseases (SCDs) are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened red blood cells (RBCs) into the tissues. **Methods:** All patients with SCDs were included. **Results:** The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher, but not acute chest syndrome (2.7% vs 3.7%), pulmonary hypertension (12.6% vs 11.7), deep venous thrombosis and/or varices and/or telangiectasias (9.0% vs 6.6%), and mean age of mortality (30.2 vs 33.3 years) in males (p>0.05 for all). **Conclusion:** The hardened RBCs-induced capillary endothelial damage, inflammation, edema, and fibrosis are initiated at birth in whole body, and terminate with diffuse tissue hypoxia and multiorgan insufficiencies even in early years of life in SCDs . Although RBCs supports and corticosteroids during emergencies and hydroxyurea therapy during whole lifespan decrease severity of diffuse capillary endothelial inflammation, edema, and fibrosis with some extent, survival shortened in both genders, dramatically. Due to the severe capillary endothelial damage all over the body, SCDs may show terminal consequences of metabolic syndrome in much earlier ages.

Keywords: Sickle Cell Diseases, Metabolic Syndrome, Hardened Red Blood Cells, Capillary Endothelial Inflammation, Capillary Endothelial Fibrosis, Atherosclerosis, Aging

INTRODUCTION

Chronic endothelial damage may be the main cause of aging and death

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by causing end-organ insufficiencies in human being [1]. Much higher blood pressures (BPs) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which eventually reduces blood supply to the terminal organs and increases systolic and decreases diastolic BPs further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death [2,3]. Although the early withdrawal of the accelerating factors can delay terminal consequences, after the development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, and dementia-like end-organ insufficiencies and aging, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the vascular process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature [4-6]. On the other hand, sickle cell diseases (SCDs) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages of life [7,8]. Hemoglobin S causes the loss of elastic and biconcave disc-shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the cases with associated thalassemia minors (TMs), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis terminating with tissue hypoxia all over the body [9]. As a difference from other causes of chronic endothelial damage, SCDs keep vascular endothelium particularly at the capillary level [10,11], since the capillary system is the main distributor of the hardened RBCs into the tissues. The hardened RBCs induced chronic endothelial damage builds up advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in SCDs [8].

MATERIAL AND METHODS

The study was performed in the Medical Faculty of Mustafa Kemal University between March 2007 and June 2016. All patients with SCDs were included. SCDs were diagnosed with hemoglobin electrophoresis performed via high-performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learned. 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. Patients with an acute painful crisis or any other inflammatory event were treated at first, and 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, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BPs of the pulmonary artery, 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 patient's complaints. So avascular necrosis of bones was diagnosed by means of MRI [12]. Associated TMs were detected with serum iron, iron-binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone [13]. Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) [14]. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% [15]. Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia [16]. An x-ray film of the abdomen in an upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. 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 the interphalangeal diameter higher than 1.0 and with the presence of Schamroth's sign [17,18]. 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 movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with echocardiographic findings, too. Stroke is diagnosed by the CT of the brain. Sickle cell retinopathy is diagnosed with an ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t-test, and comparison of proportions were used as the methods of statistical analyses.

RESULTS

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBCs in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher but not ACS (2.7% vs 3.7%), PHT (12.6% vs 11.7), DVT and/or varices and/or telangiectasias (9.0% vs 6.6%), and mean age of mortality (30.2 vs 33.3 years) in males (p>0.05 for all) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

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)
Associated TMs‡	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) ‡Thalassemia minor

Table 2. Associated pathologies of the study cases

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)
Transfused units of RBCs‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***≤0.001***	***1.4% (3)***
COPD§	***25.2% (56)***	***≤0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***≤0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***≤0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***≤0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***≤0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***≤0.05***	***13.2% (28)***
CRD**	***9.9% (22)***	***≤0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***≤0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
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 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)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

DISCUSSION

Acute painful crises are the most disabling symptoms of SCDs. Although some authors reported that pain itself may not be life-threatening, infections, medical or surgical emergencies, and emotional stress-like factors are the most common precipitating factors of the crises [19]. The increased basal metabolic rate during such additional stresses aggravates capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is significantly higher during such crises. The deaths in SCDs can not be explained by a solitary reason alone, instead, they may have a multisystemic nature. Actually, each painful crisis may complicate the following crises by leaving some sequelae on the capillary endothelial system. After a period of time, the sequelae may terminate with sudden end-organ insufficiencies. On the other hand, pain is the result of a complex and poorly understood interaction between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis of the crises by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on endothelium are of particular interest with regard to cerebrovascular diseases in SCDs . For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of SCDs [20], and it was associated with the risk of stroke in a cohort of Jamaican patients [21]. Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take the role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them [22], but according to our practice, simple and repeated RBCs transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of SCDs .

The deaths seem sudden and unexpected events in SCDs. Unfortunately, most of the deaths develop just after hospital admission, and majority of them are patients without hydroxyurea therapy [23,24]. Rapid RBCs supports are usually life-saving for such cases but preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in terminal cases due to the repeated transfusions induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismatch. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in SCDs [23,24]. According to our experiences, simple and repeated transfusions are superior to RBCs exchange in SCDs [25,26]. First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher 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 RBCs suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBCs transfusions probably have the strongest analgesic effects during the crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs 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 RBCs suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices.

Hydroxyurea may be the only life-saving drug for the treatment of SCDs . It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in SCDs [27,28]. By this way, the chronic inflammatory and destructive process of SCDs is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body [29]. Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels [30]. The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo [31]. The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations [31]. In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates [31]. But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year [31]. Whereas we used all subtypes of SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) in the previous study [24]. Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period [32]. Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival [32]. The complications start to be seen even in infancy in SCDs . For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them [33]. Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult.

ACS is a significant cause of mortality in SCDs [34]. It occurs most often as a single episode, and a past history is associated with a high mortality rate [34]. Similarly, all of 14 cases with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs 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 two to four years of age, and its incidence decreases with aging [35]. As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the cases with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of SCDs , and the incidence of ACS is higher in severe cases such as cases with SCA and higher WBCs counts [34,35]. According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ insufficiencies. ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the abnormal RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs [36]. Similarly, we strongly recommend hydroxyurea therapy for all patients with SCDs that may also be the cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% of cases [34,35], and 12 of 27 cases with ACS had evidence of fat embolism in the other study [37]. Beside that some authors indicated that antibiotics do not shorten the clinical course [38]. RBCs support must be given early in the course of ACS. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling, capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, tissue hypoxia, and end-organ insufficiencies in whole body.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT [39]. The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization, there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms [40]. PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years [41]. Onset is typically seen between 20 and 60 years of age [40]. The most common causes are CHD and COPD [40,42]. The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy [43]. But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone [43]. In fact, all layers of the vessel wall appear to be involved with prominent intimal changes [43]. The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke [43]. On the other hand, PHT is also a common consequence of SCDs [44], and its prevalence was detected between 20% and 40% in SCDs [45]. Whereas, we detected the ratio as 12.2% in the present study. Although the higher prevalences of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic risk factors or consequences in male gender, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic natures of PHT and ACS in SCDs in the present study. Additionally, frequencies of DVT and/or varices and/or telangiectasias were similar in males and females parallel to ACS and PHT (9.0% vs 6.6%, $p>0.05$, respectively). Similarly, CHD is the other most common cause of PHT in the society [46], and although the higher prevalence of CHD in males in the present study (18.0% vs 13.2%, $p<0.05$), PHT was not higher in males, again. In another definition, PHT may have a hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in SCDs [47,48], since the mean age of ACS is lower than PHT (30.3 and 34.0 years, $p<0.05$), and its mortality is much higher than PHT [34,35,40].

COPD is the third leading cause of death with various underlying etiologies in whole world [49,50]. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess weight, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Beside smoking, regular alcohol consumption is also important for the pulmonary and systemic inflammatory process of COPD, since COPD was one of the most common diagnoses in alcohol dependence [51]. Furthermore, 30-day readmission rates were higher in COPD patients with alcoholism [52]. Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD [53,54]. For example, there may be close relationships between COPD, CHD, PAD, and stroke [55]. Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in COPD, and CHD was the most common cause in a multi-center study of 5.887 smokers [56]. When the hospitalizations were researched, the most common causes were cardiovascular diseases, again [56]. In another study, 27% of mortality cases were due to cardiovascular diseases in moderate and severe COPD [57]. On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBCs in SCDs [49].

Digital clubbing is characterized by the increased normal angle of 165° between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger [58]. Although the exact cause and significance is unknown, chronic tissue hypoxia is highly suspected [59]. In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years [18]. But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia [5]. As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in 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 SCDs . Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional role of male gender in the systemic atherosclerotic process.

Leg ulcers are seen in 10% to 20% of SCDs , and the ratio was 13.5% in the present study [60]. Its prevalence increases with aging, male gender, and SCA [61]. Similarly, its ratio was higher in males (19.8% vs 7.0%, $p<0.001$), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, $p<0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year [60]. As an evidence of their atherosclerotic nature, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow [60]. The hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major causes, again [61]. 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 SCDs . The hardened RBCs induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in SCDs [62]. 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 [11]. Its main action may be the suppression of hyperproliferative WBCs and PLTs in SCDs [63]. 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 WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage [30]. According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts induced exaggerated capillary endothelial inflammation and edema instead of the fibrosis, yet.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 [6]. 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 became the most common cause of chronic liver disease even at childhood, nowadays [64]. NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis [64]. Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases [65]. Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) [66]. NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs [67]. Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD [68]. Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body [69]. 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 [69,70]. As a result, cirrhosis may also be another atherosclerotic consequence of SCDs .

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world [71,72]. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation [73]. For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BPs ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT [72]. 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 BPs with excess weight [74]. Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption [74]. However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage [75]. With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much more easily [74]. On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD [76]. Although some authors reported that alcohol was not related with the CRD [76], 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 processes may also terminate with the accelerated atherosclerosis in the renal vasculature [69]. Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke [77]. For example, the most common cause of death was the cardiovascular diseases in the CRD again [78]. The hardened RBCs-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in SCDs . In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCDs, again [79].

Stroke is an important cause of death, and develops as an acute thromboembolic event on the chronic atherosclerotic background in most of the cases. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is also a common complication of SCDs [80,81]. Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBCs counts [82]. Sickling induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis [83]. Probably, stroke may not have a macrovascular origin in SCDs , and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBCs and PLTs counts-induced exaggerated capillary inflammation, edema, and fibrosis [36].

The venous endothelium is also involved in SCDs [84]. Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, therefore physical examination must be performed in upright position. Although the relatively younger mean ages of the patients and significantly lower body mass index of SCDs patients in the literature [10], the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, p>0.05, respectively), indicating an additional venous involvement of SCDs . Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation [85]. It is an emergency since repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis [85]. It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency [86,87]. Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types [88]. Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in SCDs , and they are very painful [85,88]. The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system [85]. Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia [85]. RBCs support is the treatment of choice in acute phase whereas hydroxyurea should be the treatment of choice in chronic phase [89]. According to our experiences, hydroxyurea is effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

CONCLUSION

The hardened RBCs-induced capillary endothelial damage, inflammation, edema, and fibrosis are initiated at birth in whole body, and terminate with diffuse tissue hypoxia and multiorgan insufficiencies even in early years of life in SCDs . Although RBCs supports and corticosteroids during emergencies and hydroxyurea therapy during whole lifespan decrease severity of diffuse capillary endothelial inflammation, edema, and fibrosis with some extent, the survival shortened in both genders, dramatically. Due to the severe capillary endothelial damage all over the body, SCDs may show terminal consequences of the metabolic syndrome in much earlier ages.

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