WORSE PROGNOSIS OF SICKLE CELL DISEASES IN MALES EVEN IN THE ABSENCE OF SMOKING AND ALCOHOL

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Abstract

Background: We tried to understand the prognosis of sickle cell diseases (SCD) in both genders.

Methods: All cases with the SCD in the absence of smoking and alcohol were included.

Results: The study included 368 patients (168 males and 200 females). Mean age (29.4 versus 30.2 years), associated thalassemia minors (72.0% versus 69.0%), and body mass index (BMI) (21.7 versus 21.6 kg/m2) were similar in males and females, respectively (p>0.05 for all). Whereas total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, p=0.002), disseminated teeth losses (4.7% versus 1.0%, p<0.001), chronic obstructive pulmonary disease (COPD) (20.8% versus 6.0%, p<0.001), ileus (5.3% versus 2.0%, p<0.01), cirrhosis (5.9% versus 1.5%, p<0.001), leg ulcers (16.0% versus 7.5%, p<0.001), digital clubbing (13.0% versus 5.5%, p<0.001), and chronic renal disease (CRD) (10.7% versus 6.5%, p<0.05) were all higher in males, significantly.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into tissues. Although the similar mean age, associated thalassemia minors, and BMI and absence of smoking and alcohol, the higher total bilirubin value of the plasma, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, and CRD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

Key words: Sickle cell diseases, male sex, chronic endothelial damage, atherosclerosis, metabolic syndrome, early aging, premature death

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the systemic atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, prolonged infections such as tuberculosis, and chronic inflammatory processes including sickle cell diseases (SCD), rheumatologic disorders, and cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level terminating with accelerated atherosclerosis induced end-organ failures in early years of life. We tried to understand the prognosis of the SCD in both genders in the present study.

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 in the absence of smoking and alcohol were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including painful crises per year, epilepsy, deep venous thrombosis, transfused units of red blood cells (RBC) in their lives, surgical operations, leg ulcers, and stroke were learnt. Due to the cumulative atherosclerotic effects of smoking and alcohol together with the SCD, current and/or previous regular smokers or drinkers at least for a period of one year were excluded from the study. A complete physical examination was performed by the Same Internist. Body mass index (BMI) of each patient was calculated by the measurements of the Same Internist instead of verbal expressions. Weight in kilogram is divided by height in meter squared. Patients with disseminated teeth loss (<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, total bilirubin, 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 of bones (AVN) was diagnosed via MRI (5). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemias show a milder clinic than the sickle cell anemia (SCA) alone (6). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (7). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (8). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (9). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (10, 11). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, the mean age, associated thalassemia minors, BMI, and consequences of the SCD 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 368 patients with the SCD (168 males and 200 females). Mean ages of the patients were similar in males and females (29.4 versus 30.2 years, respectively, p>0.05). Prevalence of associated thalassemia minors were also similar in both genders (72.0% versus 69.0%, respectively, p>0.05). Mean values of BMI were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, p>0.05) (Table 1). On the other hand, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of RBC in their lives (46.8 versus 29.2, p=0.002), disseminated teeth losses (4.7% versus 1.0%, p<0.001), COPD (20.8% versus 6.0%, p<0.001), ileus (5.3% versus 2.0%, p<0.01), cirrhosis (5.9% versus 1.5%, p<0.001), leg ulcers (16.0% versus 7.5%, p<0.001), digital clubbing (13.0% versus 5.5%, p<0.001), and CRD (10.7% versus 6.5%, p<0.05) were all higher in males, significantly. Although the overall mortality was higher in males during the ten-year follow up period (8.3% versus 6.5%, p>0.05), the difference was nonsignificant probably due to the small sample size of the mortality cases. Similarly, although the mean age of mortality cases was lower in males, the difference was nonsignificant (29.0 versus 32.5 years, p>0.05) probably due to the same reason again (Table 2).

Table 1: Characteristics of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	45.6% (168)		54.3% (200)
Mean age (year)	29.4 ±9.9 (5-58)	Ns†	30.2 ±9.9 (8-59)
Associated thalassemiaminors	72.0% (121)	Ns	69.0% (138)
BMI‡ (kg/m²)	21.7 ±3.5 (14.3-32.5)	Ns	21.6 ±3.7 (14.5-46.4)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index

Table 2: Associated pathologies of the study patients according to the gender distribution

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ±7.0 (0-36)	Ns†	5.0 ±8.7 (0-52)
Total bilirubin (mg/dL)	*5.2 ± 4.9 (0.6-29.0)*	*0.011*	*4.0 ± 3.4 (0.6-22.9)*
Transfused units of RBC‡	*46.8 ± 61.0 (0-434)*	*0.002*	*29.2 ± 36.5 (0-206)*
Disseminated teeth losses (< 20 teeth present)	*4.7% (8)*	*<0.001*	*1.0% (2)*
COPD§	*20.8% (35)*	*<0.001*	*6.0% (12)*
Ileus	*5.3% (9)*	*<0.01*	*2.0% (4)*
Cirrhosis	*5.9% (10)*	*<0.001*	*1.5% (3)*
Leg ulcers	*16.0% (27)*	*<0.001*	*7.5% (15)*
Digital clubbing	*13.0% (22)*	*<0.001*	*5.5% (11)*
CHD¶	16.0% (27)	Ns	13.0% (26)
*CRD***	*10.7% (18)*	*<0.05*	*6.5% (13)*
Stroke	8.3% (14)	Ns	6.5% (13)
PHT****	10.1% (17)	Ns	12.5% (25)
Autosplenectomy	47.6% (80)	Ns	52.5% (105)
Deep venous thrombosis or varices or telangiectasias	7.1% (12)	Ns	5.5% (11)
Rheumatic heart disease	7.7% (13)	Ns	5.5% (11)
AVN*****	25.0% (42)	Ns	27.0% (54)
Sickle cell retinopathy	1.1% (2)	Ns	0.5% (1)
Epilepsy	2.9% (5)	Ns	2.5% (5)
Acute chest syndrome	2.3% (4)	Ns	3.5% (7)
Mortality	8.3% (14)	Ns	6.5% (13)
Mean age of mortality (year)	29.0 ±6.9 (19-42)	Ns	32.5 ±9.0 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Avascular necrosis of bones

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (12, 13). Hemoglobin S causes loss of elastic and biconcave disc shaped bodies of RBC. Probably loss of elasticity instead of shape is the major pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minors (6), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan but it is exaggerated with 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 all over the body (14, 15). The SCD may keep vascular endothelium particularly at the capillary level (16), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (17), whereas they were 29.0 versus 32.5 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 (18). Actually, RBC supports must be given immediately during all medical or surgical situations in which there is evidence of clinical deterioration in the SCD (9). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, and edema and the subsequent tissue hypoxia all over the body.

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (19). Its atherosclerotic effects are the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels, and it has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products by means of the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Despite its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (20). There may be an increased energy expenditure during smoking (21), and nicotine may decrease caloric intake in a dose-related manner (22). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (23). BMI seems to be the highest in former, the lowest in current, and medium in never smokers (24). Similarly, smoking may also show the weakness of volition to control eating, and prevalence of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (25). On the other hand, smoking-induced endothelial damage may increase plasma triglycerides (26), since triglycerides may behave acute phase reactants and plasma values may not be negatively affected by pathologic weight loss (27, 28). Additionally, although CHD were detected with similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalence of BMI and its consequences including dyslipidemia, HT, and DM in females (19). Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we think of some antidepressant properties of smoking and alcohol, the higher prevalence of them in males may also show some additional stresses on male sex in life and a shorthened survival (29).

Probably alcohol causes a vascular endothelial inflammation all over the body, too (30). Smoking and alcohol restrictions were the cause of female predominancy in the present study since both of them are much higher in males (29). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages which damage organs via oxidative stresses, and these effects lie far beyond lungs and liver. Against the harmful effects of the ROS, there are various enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase, and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (31). Both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats (31), and tobacco smoke had the strongest effect on protein nitrozylation in the brain (31). Ethyl alcohol affected glutathione levels in serum, kidney, and brain and superoxide dismutase activity in the brain (31). Vascular endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was higher among aborigines with alcohol dependence (32). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats (33). Probably, cirrhosis also has a capillary endothelial inflammation terminating with disseminated hepatic destruction, and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells were proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue in cirrhosis (34). Although the atherosclerotic effect of alcohol is the most obviously seen in the liver due to

the highest concentrations of its products via the portal blood flow there (30), alcohol may even cause COPD, digital clubbing, CRD, PAD, CHD, stroke, and cancers-like other atherosclerotic endpoints by the transport of its products in the blood.

COPD is the third leading cause of death in the world (35). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes of COPD. Regular alcohol consumption may also be important in the inflammatory process of COPD. For example, COPD was one of the most frequent diagnoses in patients with alcohol dependence (36). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (37). Probably an accelerated atherosclerotic process is the major structural background of functional changes seen in the COPD. The inflammatory process on vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (38, 39). For example, there may be close relationships between COPD, CHD, PAD, and stroke (40). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in COPD, and the CHD was the most common cause in a multi-center study of 5,887 smokers (41). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (41). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (42). Similarly, COPD may just be one of the terminal endpoints including priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD (43).

Digital clubbing is characterized by an increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (44). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (45). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (11). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, renal, and hepatic disorders which are characterized by chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs that affect each other in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD and its prevalence was 10.8% in the previous study (29). 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 clubbing in males in the present study (13.0% versus 5.5%, $p<0.001$) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (46), and the ratio was 11.4% in the present study. Its incidence increases with age, male sex, and SCA alone (47). Similarly, its ratio was higher in males (16.0% versus 7.5%, $p<0.001$), and mean age of the patients with leg ulcers was significantly higher than the others (34.6 versus 29.2 years, $p<0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (46). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (46). 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 (47). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood probably delays wound and fracture healing in the lower extremities. Beside the hardened bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are much more common in males (29). Hydroxyurea is the first drug that was approved by Food and Drug Administration for the treatment of SCD (16). 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 (18). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (48). Although presence of continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (49). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD.

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 (4). Although the improvement 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 at the moment (50). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and

an accelerated atherosclerosis (50). Beside terminating with cirrhosis, NAFLD is associated with a higher overall mortality rate as well as an increased prevalence of cardiovascular diseases (51). Authors reported independent associations between the NAFLD and an impaired flow-mediated vasodilation and an increased mean carotid artery intima-media thickness (CIMT) (52). The NAFLD may be considered as the hepatic consequence of the metabolic syndrome and SCD (53). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease (54). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerotic process all over the body including the liver (55). For example, chronic hepatitis C virus infection raised CIMT (55). As a result, similar with the disseminated teeth losses, COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, and AVN, cirrhosis may actually be one of the several atherosclerotic endpoints of the SCD and metabolic syndrome.

CRD is increasing all over the world, too (56). The increased prevalence and complications of the CRD may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world (57). Excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and aging may be the major underlying causes of the endothelial inflammation of the kidneys. The inflammatory process is enhanced by releases of various chemicals by lymphocytes to repair the damaged renal endothelium, particularly the endothelial cells of renal arteriols. Secondary to the continuous irritation of the endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, tissue hypoxia, and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses for acceleration of tissue inflammation and immune cell activation (58). For example, age (p= 0.04), high-sensitivity C-reactive protein (p= 0.01), mean arterial BP (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (57). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the 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 (59). Excess weight also causes renal vasodilation and glomerular hyperfiltration thatinitially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (59). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (60). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron functions, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (59). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (61). Similarly, although some authors reported that alcohol was not associated with the CRD (61), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys while damaging the renal vascular endothelium. Chronic inflammatory and infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (55). On the other hand, although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic endpoints of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (62). For example, the most common cause of death was the cardiovascular diseases in the CRD rather than the renal failure again (63). In another definition, CRD may just be one of the several atherosclerotic endpoints of the metabolic syndrome and SCD again (64).

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 the hardened RBC into the tissues. Although the similar mean age, associated thalassemia minors, and BMI and absence of smoking and alcohol, the higher total bilirubin value of the plasma, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, and CRD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

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