

# Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries

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## Abstract

**Background:** Sickle cell diseases (SCD) are severe inflammatory processes on vascular endothelium, particularly at the capillaries since the capillary system is the main distributor of hardened red blood cells into the tissues. Similarly, coronavirus disease (COVID-19) may also be a genetically determined inflammatory process particularly in pulmonary capillaries with much higher mortality rates in some families.

**Methods:** All patients with the SCD were studied.

**Results:** The study included 222 males and 212 females with similar mean ages (30.8 versus 30.3 years,  $p > 0.05$ , respectively). Smoking (23.8% versus 6.1%,  $p < 0.001$ ), alcohol (4.9% versus 0.4%,  $p < 0.001$ ), disseminated teeth losses (5.4% versus 1.4%,  $p < 0.001$ ), 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%,  $p < 0.05$ ), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%,  $p < 0.001$ ), and stroke (12.1% versus 7.5%,  $p < 0.05$ ) were all higher but not acute chest syndrome (ACS), in males (2.7% versus 3.7%,  $p > 0.05$ ).

**Conclusion:** Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic end-points were all higher in males, prevalence of ACS was similar in both genders. In another definition, ACS and severe COVID-19 may be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries, and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment.

**Key words:** Acute chest syndrome, coronavirus disease, exaggerated immune response syndromes, sickle cell diseases, capillary endothelial inflammation, capillary endothelial edema, tissue hypoxia

## Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1). Much higher blood pressures (BP) 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 venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, and they eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (4-6). On the other hand, sickle cell diseases (SCD) are a chronic inflammatory process on vascular endothelium, initiated at birth and terminated with accelerated atherosclerosis induced end-organ failures in both genders (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheral blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hardened RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened cells into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early years of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in

such patients (8). Similarly, coronavirus disease (COVID-19) may actually be a genetically determined inflammatory process, particularly involving the pulmonary capillaries with much higher mortality rates in some families.

## 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. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, 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 BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minors show a milder clinical presentation than the sickle cell anemia (SCA) alone (13). Systolic BP of the pulmonary artery of  $\geq 40$  mmHg are accepted as PHT (14). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of <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 abdomen in 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  $\geq 1.3$  mg/dL in males and  $\geq 1.2$  mg/dL 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  $>1.0$ , 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 the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sick cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, autosplenectomy, DVT and/or varices and/or telangiectasias, rheumatic heart disease, avascular necrosis of bones, sickle cell retinopathy, epilepsy, ACS, mortality, and mean age of mortality 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). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years,  $p>0.05$ , respectively). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%,  $p>0.05$ , respectively). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly ( $p<0.001$  for both) (Table 1). Similarly, transfused units of RBC in their lives (48.1 versus 28.5,  $p=0.000$ ), disseminated teeth losses (5.4% versus 1.4%,  $p<0.001$ ), 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%,  $p<0.05$ ), COPD (25.2% versus 7.0%,  $p<0.001$ ), and stroke (12.1% versus 7.5%,  $p<0.05$ ) were all higher in males, significantly. On the other hand, prevalence of ACS (2.7% versus 3.7%,  $p>0.05$ ), PHT (12.6% versus 11.7,  $p>0.05$ ), and DVT and/or varices and/or telangiectasias were similar in both genders (9.0% versus 6.6%,  $p>0.05$ ), significantly (Table 2). Beside that when we look at the mean ages of the consequences, they were 30.3 and 34.0 years ( $p<0.05$ ) in the ACS and PHT, respectively (Table 3).

Table 1: Characteristic features of the study cases

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)
<b><u>Smoking</u></b>	<b><u>23.8% (53)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>6.1% (13)</u></b>
<b><u>Alcoholism</u></b>	<b><u>4.9% (11)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>0.4% (1)</u></b>

\*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

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)
<b><u>Transfused units of RBC‡</u></b>	<b><u>48.1 ± 61.8 (0-434)</u></b>	<b><u>0.000</u></b>	<b><u>28.5 ± 35.8 (0-206)</u></b>
<b><u>Disseminated teeth losses (&lt;20 teeth present)</u></b>	<b><u>5.4% (12)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>1.4% (3)</u></b>
<b><u>COPD§</u></b>	<b><u>25.2% (56)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>7.0% (15)</u></b>
<b><u>Ileus</u></b>	<b><u>7.2% (16)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>1.4% (3)</u></b>
<b><u>Cirrhosis</u></b>	<b><u>8.1% (18)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>1.8% (4)</u></b>
<b><u>Leg ulcers</u></b>	<b><u>19.8% (44)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>7.0% (15)</u></b>
<b><u>Digital clubbing</u></b>	<b><u>14.8% (33)</u></b>	<b><u>&lt;0.001</u></b>	<b><u>6.6% (14)</u></b>
<b><u>CHD¶</u></b>	<b><u>18.0% (40)</u></b>	<b><u>&lt;0.05</u></b>	<b><u>13.2% (28)</u></b>
<b><u>CRD**</u></b>	<b><u>9.9% (22)</u></b>	<b><u>&lt;0.05</u></b>	<b><u>6.1% (13)</u></b>
<b><u>Stroke</u></b>	<b><u>12.1% (27)</u></b>	<b><u>&lt;0.05</u></b>	<b><u>7.5% (16)</u></b>
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)

\*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

## Discussion

ACS is a significant cause of mortality in the SCD (19). It occurs most often as a single episode, and a past history is associated with a high mortality rate (19). 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 aging (20). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, too, and the mean ages of the ACS and SCD were similar (30.3 and 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. Probably, ACS shows an inborn severity of the SCD, and the incidence of ACS is higher in severe cases such as cases with the SCA or higher white blood cells (WBC) counts (19, 20). According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and vascular endothelial damage, and terminates with end-organ insufficiencies. ACS may also be a collapse of the lungs during such infections, and an exaggerated immune response syndrome against the abnormal RBC-induced diffuse endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCD 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 WBC and platelets (PLT) (21). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD which 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, ACS did not show an infectious etiology in 66% of cases (19, 20), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (22). Beside that some authors indicated that antibiotics do not shorten the clinical course (16, 23). Actually, some viral causes as in the COVID-19 may also be important here, and the actual causes of the exaggerated immune response are such viruses, and the anti-inflammatory and immunomodulatory drugs including dexamethasone may be important for the treatment of ACS, too. On the other hand, RBC support must be given early in the course of ACS 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 endothelial damage, not in the lungs alone instead all over the body. According to our observations, simple and repeated transfusions are superior to RBC exchange (24, 25). First of all, preparation of one or two units of RBC 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 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 by transfusions may also indicate 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 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.

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most patients will experience mild to moderate respiratory disease, and recover without a need for special treatment. However, some cases become seriously sick. Older individuals and those with underlying diseases such as SCD, HT, DM, PAD, COPD, CHD, CRD, cirrhosis, stroke, rheumatological disorders, or cancers are more likely to develop serious illness. But actually anyone can get the disease with COVID-19 and become seriously ill or die at any age even in the absence of the above predisposing factors. Genetic susceptibility may be one of the major risk factors to have the severe form of the disease since the COVID-19 mortality rates may be much higher in some families. And probably a genetically determined exaggerated immune response syndrome against the virus may be the chief underlying cause of the severity as in the ACS and rheumatic disorders. As in the ACS, probably the disease keeps whole body circulation but the respiratory capillaries are involved, particularly due to the highest viral load in them. This mechanism may also explain the pathophysiology of ACS, and there may be a superimposed viral infection involving the respiratory system. On the other hand, the capillary system of the respiratory tract may be the most sensitive capillaries against the immune damage in the body. The highest prevalence of lung cancers in both genders among all of the other cancers may also support the hypothesis. So both the ACS and severe COVID-19 may prominently be a vasculitis, and the anti-inflammatory and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment. On the other hand, since the virus is changing its genetic codes continuously, probably all people will get the disease several times with different severity in their lives. Thus the chance of getting a severe form of the disease is always present for all individuals in the world. Even such an infection superimposed on aging or several predisposing factors induced atherosclerotic end-points may be the terminal drop of life for all individuals.

PHT is a condition of increased BP 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  $\geq 25$  mmHg. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (26). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (27). Onset is typically seen between 20 and 60 years of age (28). The most common causes are left heart diseases and chronic inflammatory pathologies of the lung, particularly CHD and COPD (28, 29). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (30). 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 (30). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (30). 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 (30). 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 (28). On the other hand, PHT is also a common consequence of the SCD (31), and its prevalence was detected between 20% and 40% in the SCD (32), whereas we detected the ratio as 12.2% in the present study. Although the higher prevalence of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic events in males, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalence of PHT and ACS in both genders also support their nonatherosclerotic nature in the SCD, here. Additionally, as a risk factor for pulmonary thromboembolic events, frequencies of DVT and/or varices and/or telangiectasias were similar in males and females (9.0% versus 6.6%,  $p > 0.05$ , respectively), parallel to ACS and PHT. Similarly, CHD is the other most common cause of PHT in society (33), and although the higher prevalence of CHD in males in the present study (18.0% versus 13.2%,  $p < 0.05$ ), PHT was not higher in them again. In another definition, PHT may have a hardened RBC-induced chronic, whereas ACS an acute thromboembolic background in the SCD (34, 35) since the mean age of ACS is much lower (30.3 and 34.0 years,  $p < 0.05$ ), and its mortality is much higher than the PHT (19, 20, 28).

COPD is the third leading cause of death with various causes all over the world (36, 37). Male gender, aging, smoking, and excess weight may be the major underlying etiologies. As also observed in the present study, regular alcohol

consumption may also be important in the pulmonary and systemic inflammatory process. For example, COPD was one of the most common diagnoses in alcohol dependence (38). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (39). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristic of COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. 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 (40, 41). For example, there may be close relationships between COPD, CHD, PAD, and stroke (42). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5,887 smokers (43). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (43). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (44). In another definition, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (36).

Digital clubbing is characterized by the increased normal angle of  $165^\circ$  between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (45). Although the exact cause and significance is unknown, chronic tissue hypoxia is highly suspected (46). 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 the pulmonary, cardiac, renal, or hepatic diseases or smoking, all of which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs and their functions are affected 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 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 show some additional role of male gender on the systemic atherosclerotic process.

Leg ulcers are seen in 10% to 20% of the SCD (47), and the ratio was 13.5%, here. Its prevalence increases with aging, male gender, and SCA (48). Similarly, its ratio was higher in males (19.8% versus 7.0%,  $p < 0.001$ ), and mean age of the leg ulcer cases was higher than the others (35.3 versus 29.8 years,  $p < 0.000$ ) in the present study. The leg ulcers have an intractable nature, and around 97% of them

relapse in a period of one year (47). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (47). The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major cause in the SCD (48). 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 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 the SCD (49). 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 WBC and PLT in the SCD (50). Although presence of a 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 (51). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts induced exaggerated endothelial inflammation, edema, and fibrosis at the capillary level.

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 in childhood nowadays (52). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (52). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (53). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (54). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (9, 55). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (56). Increased oxidative

stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol are prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (57). 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 (57, 58). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among the systemic atherosclerotic consequences of the SCD.

The increased frequency of CRD may be explained by aging of the human being as well as increased prevalence of excess weight, all over the world (59, 60). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes 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 renal tissues, especially endothelial cells of the renal arterioles. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis and tissue hypoxia and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (61). 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 (60). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (62). 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 (62). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (63). 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 (62). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (64). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (64), 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 on the renal



endothelium (57). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (65). For example, the most common cause of death was the cardiovascular diseases in the CRD (66). In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD too (67).

Stroke is an important cause of death, and an acute thromboembolic event on the atherosclerotic background is the most common cause. Male gender, aging, smoking, alcohol, and excess weight and its consequences may be the major triggering causes. Stroke is also a common complication of the SCD (68, 69). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (50, 70). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, and fibrosis (71). Probably, stroke is a terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation, edema, and fibrosis may be much more important. Infections and other stresses may precipitate the stroke, since increased metabolic rate during such events may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases develop secondary to the increased WBC and PLT induced exaggerated capillary inflammation, edema, and fibrosis (21).

The venous endothelium is also involved in the SCD (72). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Normally, leg muscles pump veins against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in upright position. Although the younger mean ages of the patients of the present study (30.8 and 30.3 years in males and females, respectively), and significantly lower body mass index of the SCD patients in the literature (10), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females,  $p > 0.05$ , respectively), indicating an additional venous involvement in the SCD. Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (73). 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 (73). It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (74, 75). Ischemic (veno-occlusive), stuttering (recurrent ischemic),

and nonischemic priapisms (arterial) are the three types of priapism (76). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood cannot return adequately from the penis as in the SCD, and they are very painful (73, 76). 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 (73). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (73). RBC support is the treatment of choice in acute phase in the SCD (77). Whereas in chronic phase, hydroxyurea should be the treatment of choice. According to experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if initiated 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

Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic end-points were all higher in males, prevalence of ACS was similar in both genders. In another definition, ACS and severe COVID-19 may be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries, and immunomodulatory drugs including dexamethasone probably should take the major role in the treatment.

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