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Mehmet Rami Helvaci *

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Research Article

Acute chest syndrome and coronavirus disease may be genetically determined exaggerated immune response syndromes in capillaries all over the body

Mehmet Rami Helvaci [1]*, Saziye Cayir [2], Hulya Halici [2], Alper Sevinc [1], Celaletdin Camci [1], Huseyin Sencan [1], Ramazan Davran [3], Abdulrazak Abyad [4], Lesley Pocock [5]

[1]Specialist of Internal Medicine, MD, Turkey.

[2]Manager of Writing and Statistics, Turkey.

[3]Assistant Professor of Radiology, MD, Turkey.

[4]Middle-East Academy for Medicine of Aging, MD, Lebanon.

[5]Medi-WORLD International, Australia.

***Corresponding Author:** Mehmet Rami Helvaci, Specialist of Internal Medicine, MD, Turkey.

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Abstract

Background: Sickle cell diseases (SCD) are severe inflammatory processes mainly on capillaries as the main distributors of hardened red blood cells (RBC) into the tissues. Moderate and severe coronavirus disease (COVID-19) may also be a genetically determined exaggerated inflammatory process on capillary endothelium all over the body terminating with high 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, $p>0.05$). Smoking ($p<0.001$), alcohol ($p<0.001$), disseminated teeth losses ($p<0.001$), ileus ($p<0.001$), cirrhosis ($p<0.001$), leg ulcers ($p<0.001$), digital clubbing ($p<0.001$), coronary heart disease (CHD) ($p<0.05$), chronic renal disease (CRD) ($p<0.05$), chronic obstructive pulmonary disease (COPD) ($p<0.001$), and stroke ($p<0.05$) were all higher but not acute chest syndrome (ACS) in males ($p>0.05$).

Conclusion: Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic risk factors or end-points were all higher in males, prevalences of ACS were similar in both genders. Although ACS and moderate and severe COVID-19 mainly affect the respiratory tract, they may be genetically determined exaggerated immune response syndromes on capillary endothelium all over the body, and immunomodulatory drugs including dexamethasone should take the major role in the treatment of moderate and severe COVID-19 and just after the RBC support in the ACS.

Keywords: acute chest syndrome; coronavirus disease; sickle cell diseases; exaggerated immune response syndromes; capillary endothelial inflammation; capillary endothelial edema; disseminated tissue hypoxia

Introduction

Chronic endothelial damage may be the major cause of aging by causing end-organ insufficiencies in human body [1]. Much higher blood pressures (BP) of the afferent vasculature may be the main accelerating factor by causing recurrent injuries on vascular endothelium. Probably, all afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those 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 such as obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric 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, aging, and 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 can not be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively [4-6]. On the other hand, sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium, initiated at birth and terminated with accelerated atherosclerosis induced end-organ failures in early years of life [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 main problem since sickling is rare in peripheric 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 inflammations, infections, and emotional stress in the body. The hardened RBC induced chronic endothelial damage, inflammation, edema, 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 capillaries which are the main distributors of the hardened RBC into the tissues [10, 11]. The hardened cells 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 them [8]. Similarly, moderate and severe coronavirus disease (COVID-19) may actually be a genetically determined exaggerated and disseminated inflammatory process on capillary endothelium all over the body terminating with high mortality rates in some families.

Material and methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were studied. 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 clinic than the sickle cell anemia (SCA) alone [13]. Systolic BP of the pulmonary artery of ≥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 ≥1.3 mg/dL in males and ≥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 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, 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). Prevalences 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**).

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

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

Table 1: Characteristic features of the study cases

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, prevalences 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**).

Variables	Male patients with SCD*	p-value	Female patients with SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** 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 2: Associated pathologies of the study cases

Beside that mean ages of all of the terminal consequences were detected (**Table 3**).

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

Table 3: Mean ages of the consequences of the sickle cell diseases

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 system. 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 capillary endothelial damage, and terminates with end-organ insufficiencies. Although ACS may be thought as a collapse of the lungs during such infections, all capillary systems of the body may probably be involved in the process, and an exaggerated and diffuse immune response syndrome against some infectious pathogens and abnormal RBC may be the cause of diffuse capillary endothelial damage, inflammation, and edema all over the body, and may even terminate with a sudden stroke or myocardial infarction. 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 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). Although the 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], and some authors indicated that antibiotics do not shorten the clinical course [23], some viral causes as in the COVID-19 may actually take role here, and the main cause of the exaggerated and diffuse immune response syndrome may be such viruses, and the anti-inflammatory and immunomodulatory drugs including dexamethasone may be important just after the RBC support in the treatment of ACS. 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 experiences, 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 more provides time to doctors 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 such as 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 that needs trained staff and additional devices. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most patients experience mild to moderate respiratory disease, and recover without a need for special treatment. However, some patients become seriously ill. 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 everybody can get the disease with COVID-19 and become seriously ill or die at any age even in the absence of the 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. As in the ACS and rheumatic disorders, a genetically determined exaggerated and disseminated immune response syndrome against the virus in capillaries all over the body may be the major underlying cause of the severity of the COVID-19. As in the ACS, the disease probably keeps whole body circulation but the respiratory capillaries are mainly involved due to the highest viral load in them. This mechanism may explain the pathophysiology of the ACS, and there may be a superimposed viral infection keeping the respiratory system in the ACS, too. On the other hand, the respiratory tract may have the most sensitive capillaries against the immune damage in the body. The highest prevalences of lung cancers in both genders among all of the other cancers may also support the hypothesis. So both of the ACS and severe COVID-19 may prominently be a vasculitis, and both of them actually keep the whole body capillary systems. Disseminated capillary inflammation and edema may accelerate tissue hypoxia, and a sudden stroke or myocardial infarction may actually be the terminal drop in both pathologies. Therefore, 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. 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 such as 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 prevalences of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic risk factors or end-

points in males, 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 their nonatherosclerotic nature in the SCD in the present study. As a risk factor for pulmonary thromboembolic events, frequencies of DVT and/or varices and/or telangiectasias were also similar in males and females (9.0% versus 6.6%, $p>0.05$, respectively), parallel to ACS and PHT in the present study. Similarly, CHD is the other most common cause of PHT in the 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 chronic, whereas ACS may have an acute inflammatory 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]. As a difference from the atherosclerotic risk factors and end-points, COVID-19-like viral infections-induced exaggerated and disseminated immune response syndromes at the capillary level may actually be important both for the PHT and ACS. COPD is the third leading cause of death all over the world [36, 37]. Male gender alone, aging, smoking, and excess weight may be the major risk factors. As also observed in the present study, regular alcohol consumption may also be important in the pulmonary and systemic inflammatory process. For instance, 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, characteristics of the 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-third 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]. So COPD may have an atherosclerotic background, and low-dose aspirin plus low-dose warfarin may be life-saving treatment regimens in moderate and severe COPD cases [45]. Similarly, 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° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger [46]. Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected [47]. 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 which are characterized with chronic tissue hypoxia [5]. As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those affect their functions 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 capillary damage, inflammation, edema, and fibrosis 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 atherosclerosis. Leg ulcers are seen in 10% to 20% of the SCD [48], and the ratio was 13.5%, here. Its prevalence increases with aging, male gender, and SCA [49]. 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 [48]. As an evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body [48]. The hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major cause in the SCD [49]. 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 leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD [50]. 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 [51]. Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the immune system. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage [52]. According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be due to increased WBC and PLT counts induced exaggerated capillary inflammation and edema instead of terminal fibrosis in early cases.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged lifespan and increased prevalence of excess weight all over the world. For instance, 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 [53]. NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process [53]. Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases [54]. Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) [55]. NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD [9, 56]. Probably smoking also takes 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 [57]. Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis in whole body [58]. 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 [58, 59]. As a result, cirrhosis may also be found among the systemic atherosclerotic consequences of the SCD.

The increased frequency of CRD may also be explained by prolonged lifespan and increased prevalence of excess weight all over the world [60, 61]. 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 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 and tissue hypoxia and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation [62]. 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 [61]. 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 [63]. Excess weight also causes renal vasodilation and glomerular hyperfiltration those initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption [63]. However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage [64]. 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 [63]. On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD [65]. 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 [65], 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 [58]. Although CRD is mainly be an advanced atherosclerotic process of the renal vasculature, there are close relationships with the other consequences of the metabolic syndrome [66]. For example, the most common causes of death were the cardiovascular diseases in the CRD again [67]. In another definition, CRD may also be one of the several atherosclerotic consequences of the metabolic syndrome and SCD [68]. 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 terminal consequences may be the major triggering causes. Stroke is also a common complication of the SCD [69, 70]. Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts [71]. Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, and fibrosis [72]. Probably, stroke is the 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, 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 stroke cases develops secondary to the increased WBC and PLT induced exaggerated inflammation, edema, and fibrosis at the capillary level [21]. The venous endothelium is also involved in the SCD [73]. For instance, varices usually occur in the lower extremities as the abnormally dilated veins with tortuous courses. Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent backward flow of blood. 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 (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 present study (9.0% versus 6.6% in males and females, p>0.05, respectively), indicating an additional venous involvement of the SCD. 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 [74]. 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 [74]. It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency [75, 76]. Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types of priapism [77]. 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 the SCD, and they are very painful [74, 77]. 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 [74]. Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia [74]. RBC support is the treatment of choice in acute phase [78, 79]. Whereas in chronic phase, hydroxyurea should be the treatment of choice. According to our experiences, hydroxyurea is an effective drug 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. As a conclusion, although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, COPD, and stroke-like atherosclerotic risk factors or end-points were all higher in males, prevalences of ACS were similar in both genders. Although ACS and moderate and severe COVID-19 mainly affect the respiratory tract, they may be genetically determined exaggerated immune response syndromes on capillary endothelium all over the body, and immunomodulatory drugs including dexamethasone should take the major role in the treatment of moderate and severe COVID-19 and just after the RBC support in the ACS.

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