ISSN: 3066-9839
Research Article

Science Set Journal of Cardiology Research

Atherosclerotic Background of Stroke in Sickle Cell Diseases

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Submitted: 22 September 2023 **Accepted:** 28 September 2023 **Published:** 05 October 2023

https://doi.org/10.63620/MKSSJCOR.2023.1013

Citation: *Helvaci, M. R., Pappel, V., Piral, K., Caylar, A., Sencan, H., Davran, R., Yaprak, M., Abyad, A., & Pocock, L. (2023). Atherosclerotic Background of Stroke in Sickle Cell Diseases. Sci Set J of Cardiology Research, 2(3), 01-14.*

Abstract

Background: *Sickle cell diseases (SCDs) are inborn and catastrophic processes on vascular endothelium, particularly at the capillaries.*

Methods: *All patients were included.*

Results: *We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Beside stroke (12.1% vs 7.5%, p<0.05), smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBCs) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), coronary heart disease (CHD) (18.0% vs 13.2%, p<0.05), and chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males, significantly (30.2 vs 33.3 years, p<0.05).*

Conclusion: *The hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multi-organ failures even at childhood. Parallel to stroke, all of the atherosclerotic risk factors or consequences including smoking, alcohol, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, and CRD were higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at the relatively younger mean age. So autosplenectomy may be a good whereas male gender alone may be a bad prognostic factor, and stroke may have an atherosclerotic background in the SCDs.*

Keywords: Sickle Cell Diseases, Hardened Red Blood Cells, Capillary Endothelial Damage, Capillary Endothelial Edema, Sudden Deaths, Atherosclerosis, Stroke

Introduction

Chronic endothelial damage may be the main underlying cause of aging and death by causing end-organ failures [1]. Much higher blood pressures (BPs) of the afferent vasculature may be the chief accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the destructive process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature.

Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures which eventually reduce blood flow to the terminal organs, and increase systolic and decrease diastolic BPs further. Some of the well-known accelerating factors of the harmful process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstruc-

tive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death [2, 3].

Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, aging, and dementia-like end-organ insufficiencies, the endothelial changes can not be reversed due to their fibrotic natures, completely.

The accelerating factors and terminal consequences of the harmful process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature [4-6]. Similarly, sickle cell diseases (SCDs) are highly destructive processes on vascular endothelium initiated at birth, and terminated with an advanced atherosclerosis-induced end-organ failures in much earlier ages of life [7, 8].

Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the patients with associated thalassemia minors (TMs), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present even at birth, but exaggerated with inflammations, infections, and emotional stress of the body. The sickled or just hardened RBCs-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, SCDs keep vascular endothelium particularly at the capillaries which are the actual distributors of the sickled or just hardened RBCs into the tissues [10, 11]. The sickled or just hardened RBCs-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ failures are the terminal results, so the life expectancy is decreased by 25 to 30 years for both genders in the SCDs [8].

Material and Methods

The clinical study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients of the SCDs were included. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Smoking and alcohol habits, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers.

A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase.

A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, marker of 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 BPs 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 was performed. Other bones for avascular necrosis were scanned according to the patients' complaints.

So avascular necrosis of bones was diagnosed via MRI [12]. Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, becuase the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone [13]. Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) [14].

The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% [15]. Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, or hypoxia [16]. An x-ray film of abdomen in upright position was taken 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. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or greater in females. Cirrhosis is diagnosed with physical examination, laboratory parameters, and ultrasonographic findings.

Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign [17, 18]. An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed for the cases with exercise electrocardiogram positivity.

So CHD is 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. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). On the other hand, transfused RBCs in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers

(19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males (30.2 vs 33.3 years, p<0.05) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

Table 1: Characteristic features of sickle cell patients

Variables	Males	p-value	Females
Prevalence	51.1% (222)	Ns*	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TMs†	72.5% (161)	Ns	67.9% (144)
Smoking	23.8% (53)	<0.001	6.1% (13)
Alcohol	4.9% (11)	<0.001	0.4% (1)

*Nonsignificant (p>0.05) †Thalassemia minors

Table 2: Associated pathologies of sickle cell patients

Variables	Males	p-value	Females
Painful crises per year	5.0 ± 7.1 (0-36)	Ns*	4.9 ± 8.6 (0-52)
Transfused units of RBCs†	48.1 ± 61.8 (0-434)	0.000	28.5 ± 35.8 (0-206)
Disseminated teeth losses (<20 teeth present)	5.4% (12)	<0.001	1.4% (3)
COPD‡	25.2% (56)	<0.001	7.0% (15)
Ileus	7.2% (16)	<0.001	1.4% (3)
Cirrhosis	8.1% (18)	<0.001	1.8% (4)
Leg ulcers	19.8% (44)	<0.001	7.0% (15)
Digital clubbing	14.8% (33)	<0.001	6.6% (14)
CHD§	18.0% (40)	<0.05	13.2% (28)
CRD¶	9.9% (22)	<0.05	6.1% (13)
Stroke	12.1% (27)	<0.05	7.5% (16)
PHT**	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	<0.05	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)	<0.05	33.3 ± 9.2 (19-47)

*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 consequences of sickle cell patients

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)

Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

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

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises [19]. Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs [20].

So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically.

Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy [21].

Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs [22].

According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs [23]. First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body.

Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers 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.

On the other hand, pain is the result of complex and poorly understood interactions between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke [24].

Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them, but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs [25].

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs [26]. It is an orally-administered, cheap, safe, and effective drug, and it may be the only life-saving drug in the treatment of the SCDs [27, 28]. It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase.

The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action

may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis [29, 30]. By this way, the inborn inflammatory and destructive process of the SCDs is suppressed with some extent.

Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As also seen in the viral hepatitis cases, although presence of a continuous damage of sickled or just hardened RBCs on the capillary endothelium, the severity of destructive process may be exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of the WBCs and PLTs may limit the capillary endothelial damage, inflammation, edema, tissue ischemia, and end-organ failures in the body [31].

Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels [32]. The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo [33]. The study particularly researched effects of hydroxyurea on the painful crises, ACS, and requirement of RBCs transfusion.

The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was started for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations. In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates. But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year [33].

Whereas we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) [28]. Parallel to our results, adults using hydroxyurea therapy for frequent painful crises appear to have a reduced mortality rate after a 9-year follow-up period [34]. The complications start to be seen even in infancy in the SCDs. For instance, infants with lower hemoglobin values were more likely to have higher incidences of clinical events such as ACS, acute painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them [35]. Hydroxyurea therapy in early years of life may improve growth, and prevent end-organ failures. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult.

On the other hand, elevations of liver enzymes during some acute painful crises can not be reversed by withdrawing of the hydroxyurea therapy alone, instead withdrawal of all of the medications were highy effective in such cases during the 20-year experience on such patients. After normalization of the liver enzymes, the essential medications must be started one by one, instead of all of them at the same time, again.

Thus hydroxyurea must even be used during the acute painful crises. Additionally, we observed mild, moderate, or even severe bone marrow suppressions and pancytopenia in some patients using high-dose hydroxyurea (35 mg/kg/day). Interestingly, such cases were completely silent other than some signs and symptoms of anemia, and all of them were resolved completely just by giving a few-day break for the hydroxyurea therapy and starting with smaller doses again.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors.

Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TXs are responsible for the aggregation of PLTs to form blood clots.

In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLTs, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke [36].

Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction [37]. According to the medical literature, aspirin may also be effective in prevention of colorectal cancers [38]. On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease [39].

The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye [40]. The syndrome mostly affects children, but it can only affect fewer than one in a million children a year. It usually starts just after recovery from a viral infection, such as influenza or chicken pox [40]. Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness. Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it [39].

Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling [40]. Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage [39]. Interestingly, about 90% of cases in children are associated with an aspirin use [41]. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years [42].

Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease [39]. When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% of Reye syndrome was seen [40]. Due to the higher side effects of corticosteroids in long term, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added with an anti-inflammatory dose even in childhood into the acute and chronic phase treatments of the SCDs [43].

ACS is a significant cause of mortality in the SCDs. It occurs most often as a single episode, and a past history is associated with a higher mortality rate [44]. Similarly, all of 14 patients with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs and ventilation supports and antibiotic therapy in the present study.

The remaining 12 patients are still alive without a recurrence at the end of the 10-year follow up period. ACS is the most common between two to four years of age, and its incidence decreases with aging [45]. As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the patients with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively).

The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of the SCDs, and the incidence of ACS is higher in severe patients such as patients with the SCA and higher WBCs counts [44, 45]. According to our long term experiences on the SCDs, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ failures-induced sudden deaths.

ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the sickled or just hardened RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs [46].

Similarly, we strongly recommend hydroxyurea for all patients that may also be the cause of low incidence of ACS in our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% (44, 45), and 12 of 27 cases with ACS had evidence of fat embolism in the other study [47]. Beside that some authors indicated that antibiotics did not shorten the clinical course [48]. RBCs support must be given as earliest as possible. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling-induced exaggerated capillary endothelial edema, disseminated tissue hypoxia, and end-organ failures-induced sudden deaths in the SCDs.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher.

An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT [49]. The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization (WHO), 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 [50].

PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years [51]. Onset is typically seen between 20 and 60 years of age [50]. The most common causes are CHD and COPD [50, 52]. The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy. 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 [53].

In fact, all layers of the vessel wall appear to be involved with prominent intimal changes [53]. 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 [53]. On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs [54, 55]. Whereas we detected the ratio as 12.2% in the present study. The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the present study. Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic consequences in male gender, and the male gender alone is being a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic backgrounds of them in the SCDs in the present study.

Similar to our result, women have up to four times of the risk of men for development of idiopathic PHT, and generally develop symptoms 10 years earlier than men in the literature with the unknown reasons, yet [56]. Although COPD and CHD are the most common causes of PHT in the society, and although COPD (25.2% vs 7.0%, $p<0.001$) and CHD (18.0% vs 13.2%, $p<0.05$) were higher in male gender in the present study, PHT was not higher in males, again [52, 57].

In another definition, PHT may have a sickled or just hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs, because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$) in the present study, but its mortality was much higher than PHT in the literature [44, 45, 50, 58, 59].

COPD is the third leading cause of death with various underlying etiologies all over the world [60, 61]. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess weight, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Beside smoking, regular alcohol consumption is also an important risk factor for the pulmonary and systemic atherosclerotic processes, since COPD was one of the most common diagnoses in alcohol dependence [62].

Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism [63]. Probably an accelerated atherosclerotic process is the main structural background of functional changes seen with the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD [64, 65].

For example, there may be close relationships between COPD, CHD, PAD, and stroke, and CHD was the most common cause of deaths in the COPD in a multi-center study of 5.887 smokers [66, 67]. When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again [67]. In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD [68]. Similarly, COPD may just be the pulmonary consequence of the systemic atherosclerotic process caused by the sickled or just hardened RBCs in the SCDs [60].

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 [69]. Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected [70]. 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 by chronic tissue hypoxia [5]. As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each other's functions in a short period of time. Similarly, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the present study.

It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillaries in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional risks of male gender in the systemic atherosclerosis.

Leg ulcers are seen in 10% to 20% of the SCDs, and the ratio was 13.5% in the present study [71]. Its prevalence increases with aging, male gender, and SCA [72]. Similarly, its ratio was higher in males (19.8% vs 7.0%, $p<0.001$), and mean age of the leg ulcer patients was higher than the remaining ones in the present study (35.3 vs 29.8 years, $p<0.000$). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year. As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply [71].

The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again [72]. Prolonged exposure to the sickled or just hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs.

The sickled or just hardened RBCs-induced venous insufficiencies may also accelerate the highly destructive 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, pooling of blood may be the main 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.

Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage [32]. Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema [31].

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States [6]. Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays [73].

NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis [73]. Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases [74].

Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) [75]. NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs [76]. Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD [77].

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 much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there.

Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body [78]. 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 [78, 79]. As a result, cirrhosis may also be another atherosclerotic consequence of the SCDs.

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world [80, 81]. Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the main underlying causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight-induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation [82].

For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BPs ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT [81]. Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BPs with excess weight [83].

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 [83]. However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (84). 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 faster [83]. On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD [85]. Although some authors reported that alcohol was not related with the CRD, various metabolites of alcohol circulate even in the renal capillaries, and give harm to the renal capillary endothelium [85]. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature [78].

Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke, and the most common cause of death was the cardiovascular diseases in the CRD again [86, 87]. The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again [88].

CHD is the most common of the cardiovascular diseases [89]. In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD [90]. Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BP, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes [91].

It is the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaques secondary to the chronic inflammation of the arteries. It can present with stable angina, unstable angina, myocardial infarction, and sudden cardiac death [89]. It is usually symptomatic with increased basal metabolic rate and emotional stress. It is the cause of deaths in 15.6% of all deaths, globally [92].

So it is the most common cause of death in the world, nowadays [92]. In the United States in 2010, about 20% of those over the age of 65 years had CHD, while it was present in 7% of those between the ages of 45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men [93]. On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment [91]. Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis [94]. Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the present study , respectively ($p<0.05$).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too [95, 96]. We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the present study, respectively ($p<0.05$).

Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts [97]. Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause inborn and severe capillary endothelial inflammation, edema, and fibrosis in the SCDs [98]. Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important [99]. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke

by increasing basal metabolic rate, sickling, and capillary endothelial edema. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs-induced exaggerated capillary endothelial inflammation and edema in the absence of prominent fibrosis, yet [46].

The venous capillary endothelium may also be involved in the SCDs [100]. Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and telangiectasias develop.

DVT may also cause varicose veins and telangiectasias. 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 the upright position. Although the relatively younger mean ages and significantly lower body mass index of the SCDs cases in the literature, the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, $p>0.05$, respectively), indicating an additional venous involvement of the SCDs [10].

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 [101]. It is an emergency because repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis [101]. It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency [102, 103].

Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types [104]. 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 SCDs, and they are very painful [101, 104]. RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases [105]. According to our experiences, hydroxyurea is highly effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillaries if initiated later in life.

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954.

In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO.

In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria.

It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings [106]. Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target INR value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 [107].

When warfarin is used and international normalised ratio (INR) is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 [108]. Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree.

A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% [109].

All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord [109]. The risk is particularly increased once the INR exceeds 4.5 (109). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin [110]. But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis [111].

In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) [111]. Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin ($p= 0.009$) [112].

Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between (p>0.05) [112]. On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTEs), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTEs in patients with CVT [113].

Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom [114]. Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients [115].

There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022). The mortality was markedly lower in the warfarin group, too (p= 0.005) (115). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) [115].

Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer [116]. The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 [116]. The average daily dose was 2.6 mg, and the mean INR was 1.5 (116). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding [117].

Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin [118]. The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study [119]. On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCDs. So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCDs [120].

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body.

It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice [121]. In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing [122]. It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups (p<0.05) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body.

So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content [123]. Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD, the prevalence of CHD was lower in females with the higher prevalence of autosplenectomy in the present study [124].

Conclusion

the hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Parallel to stroke, all of the atherosclerotic risk factors or consequences including smoking, alcohol, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, and CRD were higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at the relatively younger mean age. So autosplenectomy may be a good whereas male gender alone may be a bad prognostic factor, and stroke may have an atherosclerotic background in the SCDs.

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