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Research Article

Acarbose Should be the First-Line Antidiabetic Agent

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Abstract

Background: Atherosclerotic endpoints may be the major cause of aging and shortened survival in human being.

Methods: All patients with sickle cell diseases (SCD) were included into the study.

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

Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage initiated at birth terminates with multiorgan failures in early decades of life in the SCD. Excess fat tissue may be much more significant than smoking and alcohol for atherosclerotic endpoints since excess fat tissue-induced diabetes mellitus is the most common cause of the CRD in human being. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is well-known. Since acarbose is a safe, cheap, oral, long-term used, and non failed drug for excess fat, and since acarbose intolerance is significantly lower than metformin in the society, acarbose should be the first-line antidiabetic agent, clinically.

Keywords: Sickle Cell Diseases; Acarbose; Metformin; Excess Fat Tissue; Capillary Endothelial İnflammation; Atherosclerotic Endpoints; Diabetes Mellitus

Introduction

Chronic endothelial damage, initiated at birth, may be the major cause of aging and death by means of the atherosclerotic endpoints in human being [1]. Much higher blood pressures (BP) of the afferent vasculature may be the strongest accelerating factor via the repeated damages on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the destructive process. Thus venosclerosis is not a significant health problem. 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 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 and mental inactivity, emotional stresses, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, mesenteric ischemia, osteoporosis, dementia, early aging, and premature death [2,3]. Although early withdrawal of the accelerating factors can delay the endpoints, the endothelial changes can not be reversed, completely due to fibrotic natures of them. The accelerating factor and atherosclerotic endpoints of the destructive process on vascular endothelium have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature [4-6]. Similarly, sickle cell diseases (SCD) are highly destructive process on vascular endothelium, initiated at birth and terminated with an accelerated atherosclerosis-induced multiorgan failures in much earlier decades of life [7,8]. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the major problem since sickling is rare in peripheric blood samples of cases with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis in human being. Loss of elasticity is present in whole lifespan, but exaggerated with inflammation, infection, cancer, or additional stresses. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body [9]. As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level since the capillary system is the main distributor of the hardened RBC [10,11]. The hardened RBC-induced chronic endothelial damage builds up an accelerated atherosclerosis in much earlier decades of life. Vascular narrowing and occlusions-induced tissue ischemia and end organ failures are the final consequences, so the mean life expectancy is decreased 30 years or more in the SCD since we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD in our clinic [8].

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were studied. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgical procedures, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Patients with a history of one pack-year and one drink-year were accepted as smoker and drinkers, respectively. A full physical examination was performed by the Same Internist, and cases with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process 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 magnetic resonance imagings (MRI) of brain and 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 TM were dete-

cted with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone [13]. Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension (PHT) [14]. Hepatic cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. 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, and 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 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 continuously elevated serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or higher in females. Digital 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 taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of a positive exercise electrocardiogram. Eventually, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke was diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p > 0.05$, respectively), and there was no patient above the age of 59 years neither in male nor in females. Associated TM were detected with similar prevalences in male and females (72.5% vs 67.9%, $p > 0.05$, respectively). Both smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males ($p < 0.001$ for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, $p = 0.000$), disseminated teeth losses (5.4% vs 1.4%, $p < 0.001$), ileus (7.2% vs 1.4%, $p < 0.001$), CRD (9.9% vs 6.1%, $p < 0.05$), cirrhosis (8.1% vs 1.8%, $p < 0.001$), COPD (25.2% vs 7.0%, $p < 0.001$), CHD (18.0% vs 13.2%, $p < 0.05$), leg ulcers (19.8% vs 7.0%, $p < 0.001$), clubbing (14.8% vs 6.6%, $p < 0.001$), and stroke (12.1% vs 7.5%, $p < 0.05$) were all higher in males. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample size of the study cases (Table 2). On the other hand, mean ages of the atherosclerotic endpoints were shown in Table 3.

Table 1: Characteristic features of the study patients.

Variables	Males with the SCD*	p-value	Females with the 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 TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	23.8% (53)	<0.001	6.1% (13)
Alcoholism	4.9% (11)	<0.001	0.4% (1)

*Sickle cell diseases †Nonsignificant ($p > 0.05$) ‡Thalassemia minors.

Table 2: Associated pathologies of the study patients.

Variables	Males with the SCD*	p-value	Females with the 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)
CHD§	18.0% (40)	<0.05	13.2% (28)
Cirrhosis	8.1% (18)	<0.001	1.8% (4)
COPD¶	25.2% (56)	<0.001	7.0% (15)
Ileus	7.2% (16)	<0.001	1.4% (3)
Leg ulcers	19.8% (44)	<0.001	7.0% (15)
Digital clubbing	14.8% (33)	<0.001	6.6% (14)
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 §Coronary heart disease ¶Chronic obstructive pulmonary disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome.

Table 3: Mean ages of endpoints of the sickle cell diseases.

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

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

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

Discussion

Excess fat tissue may be the most common cause of vasculitis all over the body. Probably, obesity is one of the irreversible endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide little benefit either to reverse obesity or to prevent its consequences. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue [19]. The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerosis may even decrease the clearance of malignant cells by the natural killers [20]. The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity [21,22]. Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) concentration in serum, since fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines [23,24]. On the other hand, individuals with excess fat tissue will also have an increased cardiac output. The prolonged increase in blood volume may aggravate myocardial hypertrophy and decrease cardiac compliance further. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol levels increased and high density lipoproteins (HDL) decreased parallel to the increased body mass index (BMI) [25]. Similarly, CHD and stroke increased parallel to the increased BMI [26]. Eventually, the risk of death from all causes increased parallel to the severity of excess fat tissue in all age groups, and the cases with underweight may even have lower biological ages and longer survival than the others [27]. Similarly, calorie restriction prolongs survival and retards age-related chronic diseases in human being [28].

Smoking may be the second most common cause of vasculitis all over the body. It may cause a systemic inflammation on vascular endothelium terminating with atherosclerotic end organ failures in early decades of life [29]. Its atherosclerotic effect is clear in the Buerger's disease and COPD [30]. Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply, particularly by walking in the feet. It typically begins in extremities but may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also

common. Skin ulcerations and gangrene of fingers or toes are the irreversible endpoints. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be the major cause in the development of Buerger's disease, particularly in the lower extremities. Multiple narrowing and occlusions in the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may be beneficial in prevention of microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP positive acute phase reactants in smokers [31]. Similarly, smoking was associated with the lower BMI values due to the systemic inflammatory effects [32,33]. An increased heart rate was detected just after smoking even at rest [34]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [35]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten [36]. Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years [37]. Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females [38]. The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking, so smoking may be more harmful for women probably due to the higher BMI in them [39]. Chemical toxicity of smoking can affect various organ systems. For instance, it is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis with several possible mechanisms [40]. First of all, smoking may have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts [41]. Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis [42]. Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI and GU tracts terminating with IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular inflammation may terminate with the GI and GU tract infections and urolithiasis since some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits. Actually, 10% of urinary stones are struvite stones those are built by magnesium ammonium phosphate produced by the urease producing bacteria. As a result, urolithiasis was seen in 17.9% of patients with the IBS and 11.6% of the patients without ($p < 0.01$) [40].

Together with the stroke, CHD is the other major cause of death in the human being. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence

of CHD [43]. Probably, excess fat tissue may be the most important cause of CHD since there are nearly 20 kg of excess fat between the lower and upper borders of normal weight, 33 kg between the obesity, 66 kg between the morbid obesity (BMI ≥ 40 kg/m^2), and 81 kg between the super obesity (BMI ≥ 45 kg/m^2) in adults. In fact, there is a huge percentage of adults with a heavier fat mass than their lean mass that brings a heavy stress both on the heart and brain.

Hepatic cirrhosis is 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 hepatic cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess fat tissue, globally. 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 at the moment [44]. NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and atherosclerotic endpoints [44]. Beside terminating with cirrhosis, NAFLD is associated with increased prevalences of CHD and stroke, and a shortened survival [45]. Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) [46]. NAFLD may be considered as one of the hepatic endpoints of the metabolic syndrome and SCD [47]. Probably smoking also takes role in the inflammatory process of the capillary endothelium in the liver because the systemic inflammatory effects of smoking on the endothelial cells is clear in Buerger's disease and COPD [36]. Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with atherosclerotic endpoints in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of alcohol and metabolites in the liver. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerotic process [48]. 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 [49]. As a result, hepatic cirrhosis may also be another atherosclerotic endpoint of the excess fat tissue, metabolic syndrome, and SCD, again.

Acute painful crises are the severest symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stresses are the most common precipitating factors of the crises [50]. The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with tissue hypoxia and multiorgan insufficiencies. So the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with multiorgan failures and sudden death with an 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 SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy [51,52]. Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD [51-53]. According to our experiences, simple and repeated transfusions are superior to RBC exchange [54,55]. First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during such crises [56]. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all

over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Terminally, 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 RBC, WBC, platelets (PLT), and endothelial cells, yet. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints in the SCD. For instance, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD, and it was associated with the risk of stroke. Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required, but according to our experiences, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden deaths which may develop secondary to multiorgan failures on the atherosclerotic endpoints of the SCD.

Hydroxyurea may be one of the life-saving drugs for the treatment of the SCD at the moment. 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 suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD. By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial cells damage-induced edema, ischemia, and infarctions all over the body. Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels. 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. The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea group that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations. 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, annually. Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7, annually ($p < 0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p < 0.000$). Parallel to us, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period. Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival. The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them. If started in early years of life, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. Although RBC transfusions can also reduce the complications, there are the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult. Thus RBC transfusions should be kept in hands just for emergencies as the most effective weapon in our hands at the moment.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of

PLT, irreversibly. This property causes aspirin being different from other NSAID, 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 inactivates the COX enzyme, irreversibly, which is required for the synthesis of prostaglandins (PG) and thromboxanes (TX). PG 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. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin irreversibly blocks the formation of TXA_2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. But aspirin does not decrease the blood viscosity. The antithrombotic property of aspirin is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke. 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. According to the literature, aspirin may also be effective in prevention of colorectal cancers. On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin should not be prescribed for febrile patients under the age of 12 years. Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease. Reye syndrome is a rapidly worsening brain disease. The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye. The syndrome mostly affects children, but it can only affect fewer than one in a million children, annually. Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness. Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen. Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage. It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use. Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s. When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen. Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD.

Warfarin is an anticoagulant, and it was the 58th most commonly prescribed medication in the United States in 2020. Warfarin does not have any effect on blood viscosity, too. It can prevent formation of blood clots and reduce the risk of thromboembolism. Warfarin is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent blood clots formation as in DVT and pulmonary embolism, and to protect against stroke in atrial fibrillation (AF), valvular heart disease, and 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 the ambulatory settings. Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalised ratio (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. When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5. Its effects can be reversed with phytomenadione (vitamin K_1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K_1. Without sufficient active vitamin K_1, 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, and these effects can last for up to five days. The consensus agrees that current self-testing and management devices are effective methods of

monitoring oral anticoagulation therapy, providing outcomes possibly better than achieved, clinically. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is just 1-3%, annually. All types of bleeding may occur, but the severest ones are those involving the central nervous system. The risk is particularly increased once the INR exceeds 4.5. The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin. Thirteen publications from 11 cohorts including more than 48.500 patients with more than 11.600 warfarin users were included in the meta-analysis in which 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 ($p > 0.05$). Similarly, warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH). Whereas recurrent ICH occured in 6.7% of patients who used warfarin and 7.7% of patients who did not use warfarin ($p > 0.05$). On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens. Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes. Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term use of low-dose warfarin is highly effective and safe with a reduction of 86% in the risk of stroke ($p = 0.0022$). The mortality rate was markedly lower in the warfarin group, too ($p = 0.005$). The frequencies of bleedings that required hospitalization or transfusion were similar in both groups ($p > 0.05$). Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value was 1.5. 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 bleedings as for warfarin, but increased GI bleeding. Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin. The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups, respectively ($p > 0.05$ for both) with AF in another study. On the other hand, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial cell edema-induced myocardial infarction and stroke may cause sudden deaths in the SCD. So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving regimen to decrease severity of capillary endothelial cell inflammation, and to prevent atherosclerotic endpoints even at childhood in the SCD.

COPD is the third leading cause of death in human being. Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the major causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints all over the body. Regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence. Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism. Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary endpoint of the systemic atherosclerotic process. 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. For instance, there may be close relationships between COPD, CHD, PAD, and stroke. 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. When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again. In another study, 27% of morta-

lity cases were due to the cardiovascular diseases in the moderate and severe COPD. Eventually, COPD may be the pulmonary endpoint of the systemic atherosclerotic process caused by the hardened RBC in the SCD.

Leg ulcers are seen in 10% to 20% of the SCD. Its prevalence increases with aging, male gender, and SCA. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year. Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes. 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 be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be 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. It is an oral, 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. Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. Similarly, lower WBC counts were associated with lower crisis rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain. Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial cell inflammation and edema.

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. Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected. 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, clubbing is frequently associated with the pulmonary, cardiac, renal and hepatic diseases, and smoking those are characterized with chronic tissue hypoxia [5]. As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, clubbing is also common in the SCD with a prevalence of 10.8% in the present study, too. It probably shows chronic tissue hypoxia caused by disseminated endothelial cell damage, inflammation, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%, $p < 0.001$) may also indicate some additional role of male gender about the atherosclerotic endpoints.

CRD is also increasing that can also be explained by aging of the human being and increased prevalence of excess weight all over the world. Aging, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarct. Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation. For instance, age ($p = 0.04$), high-sensitivity CRP ($p = 0.01$), mean arterial BP ($p = 0.003$), and DM ($p = 0.02$) had significant correlations with the CIMT. 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 fat tissue. Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the

increased tubular reabsorption. However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage. With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM, CRD progresses much more easily. On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD. Although some authors reported that alcohol was not related with the CRD, various metabolites of alcohol circulate in blood vessels of kidneys and give harm to the endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature. Due to the systemic nature of atherosclerosis, there are close relationships between CRD and other atherosclerotic endpoints of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke. For example, the most common causes of death were the CHD and stroke in the CRD, again. The hardened RBC-induced capillary endothelial damage cell may be the major cause of CRD in the SCD, again.

Together with the CHD, stroke is the other final cause of death, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious processes, cancers, and emotional stress may be the major underlying causes. Stroke is also a common atherosclerotic endpoint of the SCD. Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts. Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial cell damage, inflammation, edema, and fibrosis. Probably, stroke does not have a macrovascular origin in the SCD, and acute onset diffuse capillary endothelial cell damage, inflammation, and edema may be much more significant. Eventually, permanent neurological deficits of stoke are rare in cases with the SCD. Infection, inflammation, medical or surgical emergency, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. Decreased stroke with hydroxyurea can also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced an acute onset accelerated capillary endothelial cell edema in the SCD.

Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. Acarbose binds to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Actually, it does not have any direct effect on glucose absorption. It should be taken with the first bite of the meal, and its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use. Acarbose failure has not been reported up to now. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, accounting for the frequency and severity of GI adverse effects such as flatulence, loose stool, and abdominal discomfort. If started with a lower dosage and titrated slowly, it tends to cause tolerable GI side effects. Long-term use increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use even in hepatic cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease the risk of carcinogenesis. After oral administration, less than 2% of the unchanged drug can enter into the circulation. Therefore there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15%. Similarly, it lowers fasting and postprandial insulin levels. The initial improvement in blood glucose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years. Its beneficial effects on serum lipids were also documented with a dose-dependent manner, since dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial

lipid metabolism. Carbohydrate-induced postprandial triglyceride synthesis is reduced for several hours, so acarbose lowers plasma triglyceride levels. The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT). Significantly elevated ursocholic acids in the stool appear to be the additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in type 2 DM. Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction. So it prevents all atherosclerotic endpoints of excess fat even in the absence of IGT or DM. Although some authors reported as opposite, it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect or toxicity.

Metformin is a biguanide currently being used worldwide. It is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption. Precise mechanism of intracellular action of metformin remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite in the previous study. Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen. According to our opinion, the major effect of metformin is a powerful inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported. Probably the major component of the metabolic syndrome may be excess fat tissue and its atherosclerotic endpoints which can be prevented by suppression of appetite. So treatment of excess fat tissue with metformin will probably prevent not only the IGT or DM but also most of the other atherosclerotic endpoints. Due to the very low risk of life threatening side effects of metformin, even we have never seen before, it can be initiated for majority of cases with excess fat tissue, but clinicians must be careful above the age of 70 years due to risks of debility induced weight loss in elders. Although 25.9% of patients stopped metformin due to an excessive anorexia, only 10.6% of patients stopped acarbose due to an excessive flatulence or loose stool in the other study. So acarbose intolerance is lower than metformin in the society ($p < 0.001$). Eventually, acarbose can be used in a larger patient population than metformin according to our clinical experiences, and we should not put a lower limit of age to start acarbose for patients with excess fat.

As a conclusion, hardened RBC-induced capillary endothelial damage initiated at birth terminates with multiorgan failures in early decades of life in the SCD. Excess fat tissue may be much more significant than smoking and alcohol for the atherosclerotic endpoints since excess fat tissue-induced DM is the most common cause of the CRD in human being. The efficacy of acarbose to lower blood glucose by preventing breakdown of starch into sugar in the small intestine is well-known. Since acarbose is a safe, cheap, oral, long-term used, and non failed drug for excess fat tissue, and since acarbose intolerance is significantly lower than metformin in the society, acarbose should be the first-line antidiabetic agent, clinically.

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