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Review Article

Sickle Cell Diseases as an Accelerated Atherosclerotic Process in Whole Body İncluding the Heart

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Abstract

Sickle cell diseases are chronic inflammatory processes on vascular endothelium at the capillary level in whole body, and terminate with accelerated atherosclerosis induced end-organ failures including the heart failure in very early years of life.

Keywords: *Sickle Cell Diseases; Chronic Endothelial Damage; Atherosclerosis; Heart Failure*

Chronic endothelial damage may be the most common type of vasculitis and the leading cause of aging, morbidity, and mortality in human being. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium, and probably whole afferent vasculature including capillaries are involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the inflammatory process are physical inactivity induced weight excess, smoking, alcohol, and other chronic inflammatory processes including rheumatologic disorders, prolonged infections, and cancers for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. Although early withdrawal of causative factors may prevent final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes can not be reversed completely due to their fibrotic natures [1]. They were researched under the title of metabolic syndrome in the literature, extensively [2,3]. Similarly, sickle cell diseases (SCDs) are chronic inflammatory processes on vascular endothelium at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem since sickling is very rare in peripheric blood samples of cases with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan but exaggerated with increased metabolic rate of the body. The hard RBCs induced chronic endothelial inflammation, edema, and fibrosis at the capillary level terminate with cellular hypoxia in all over the body [4,5]. Capillary vessels are mainly involved in the process due to their distribution function for the hard bodies.

As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium at the capillary level [6], since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature [7]. Delayed diagnosis of the diseases, delayed initiation

of hydroxyurea therapy, and inadequate RBC supports during medical and surgical emergencies shorten the lifespan. Actually, RBC supports must be given immediately during all medical or surgical events in which there is an evidence of clinical deterioration in the SCDs [8,9]. RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body. According to our ten-year experiences, simple RBC transfusions may be superior to exchange. 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 patients. Secondly, transfusion of one or two units of RBC suspensions in each time decreases the severity of pain and relaxes anxiety of the patients and families in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions in each time will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent deaths developed during transport to tertiary centers for the exchange.

Excessive fat accumulation in hepatocytes is called as hepatosteatosis. It is usually accepted as one of the hepatic manifestations of metabolic syndrome. It may progress to non-alcoholic fatty liver disease (NAFLD), steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and hepatic failure. Blocking triglyceride secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms [10]. Hepatosteatosis may actually be one of the consequences of chronic inflammatory processes including physical inactivity induced weight excess, smoking, alcohol, infections, cancers, and other inflammatory disorders, and is strongly associated with an accelerated atherosclerotic process not only in the liver instead all over the body. For example, hepatosteatosis is seen in one-third of cases with hepatitis B virus-related chronic liver disease [11]. Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas [12]. The liver density measurement on contrast abdominopelvic computed tomography of colorectal cancer cases was low that is consistent with NAFLD [13]. As an acute phase reactant, serum thrombopoietin levels increased in patients with NAFLD [14]. Although serum levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in patients with NAFLD [15]. As a result, hepatosteatosis is associated with an impaired carotid intima-media thickness (CIMT) and flow-mediated dilation that are considered as early markers of atherosclerosis [16]. Furthermore, patients with NAFLD have more complex CAD [17]. CIMT was correlated with BMI ($P < 0.001$), age ($P= 0.001$), and grade 2 - 3 NAFLD ($P < 0.001$), and CIMT and grade 2 - 3 NAFLD were associated with the severity of CAD ($P < 0.001$ for both) [18]. Similarly, NAFLD was correlated with the severity of CAD and CIMT in another study ($P < 0.001$ for both) [19]. As a result, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume while the degree of hepatosteatosis was increasing [20]. Additionally, degree of hepatosteatosis was correlated with the right ventricular diastolic dysfunction [21]. According to our opinion, hepatosteatosis may actually be one of hepatic consequences of the systemic atherosclerotic process of the SCDs.

COPD is the third leading cause of mortality in the world [22]. It is an inflammatory disorder mainly affecting the pulmonary vasculature, and physical inactivity induced weight excess, smoking, and aging may be the major causes. Probably regular alcohol consumption also takes role in the inflammatory process. Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study [23]. Additionally, 30-day readmission rate to the hospitals was higher in COPD patients with alcoholism [24]. Probably an accelerated atherosclerotic process is the main structural background of the COPD. The endothelial process is enhanced by release of various chemicals by inflammatory cells, and terminates with endothelial fibrosis and tissue losses in the lungs. Although COPD may mainly be thought as an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of a disseminated endothelial inflammation all over the body, and close relationships were observed between COPD, CAD, PAD, and stroke [25,26]. Two-third of mortality cases were caused by cardiovascular diseases and lung cancers in smokers, and when the hospitalizations were researched, the most common causes were the cardiovascular diseases again [27]. Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases [28]. Due to the strong atherosclerotic natures of the SCDs and COPD, COPD may be one of the terminal consequences of the SCDs due to the higher prevalences of priapism, leg ulcers, digital clubbing, CAD, CRD, and stroke in the COPD group in another study [29].

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers [30]. Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease has never been reported in the absence of smoking. Smoking induced endothelial damage may be much more severe in the pulmonary vasculature due to the much higher concentration of its products here. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products by means of the blood. COPD may be Buerger's disease of the lungs. Beside the strong atherosclerotic effects, smoking in human being and nicotine in animals may be associated with some weight loss [31]. There may be an increased energy expenditure during smoking [32], and nicotine may decrease caloric intake in a dose-related manner [33]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten [34]. Similarly, BMI seems to be the highest in the former and the lowest in the current smokers [35]. As a pleasure in life, smoking may also show the weakness of volition to control eating. For example, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome [36]. Additionally, although CAD was detected with similar prevalences in males and females, smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females [30]. Probably toxic substances of tobacco smoke cause a diffuse inflammation on vascular endothelium all over the body, and the inflammation may be the major cause of loss of appetite during circulation of the substances within the blood since body does not want to eat anything during fighting. So regular smoking comes with a prominent weight loss, clinically.

Digital clubbing should alert physicians about some systemic disorders [1]. It is characterized by loss of normal < 165° angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger [37]. Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine [8], whereas the prevalence was 4.2% in the same department in our university [1]. The exact cause and significance is unknown but chronic tissue hypoxia has been suspected [38]. In the above study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years [8]. According to our opinions, digital clubbing is frequently associated with pulmonary, cardiac, and/or hepatic disorders or smoking that are featuring with chronic tissue hypoxia since lungs, heart, and liver are closely related organs that affect each other in a short period of time. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis at the capillary level in the SCDs.

Leg ulcers are seen in 10 to 20% of patients with the SCDs [39]. Its incidence increases with age, male sex, and HbSS genotype [39]. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in one year [40]. As an evidence of their atherosclerotic background, the leg ulcers occur in distal areas with less collateral blood flow in the body [40]. The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause [39]. Prolonged exposure to the hard bodies due to blood pooling in the lower extremities may also explain the leg but not arm ulcers. The hard RBCs induced venous insufficiencies may also accelerate the process by accelerating pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have effects on the venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have some effects on the leg ulcers since both of them are much more common in males, and their atherosclerotic effects are obvious in the COPD, Buerger's disease, and cirrhosis [39]. According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial inflammation and edema at the capillary level in the SCDs.

Stroke is also a common complication of the SCDs [41]. Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count [42,43]. Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain [43]. Stroke may not have a macrovascular origin instead generalized endothelial inflammation and edema at the capillary level may be much more important in the SCDs. Infections, serious injuries, other inflammatory disorders, and stresses may precipitate the stroke since increased metabolic rate during such events may accelerate sickling and secondary endothelial inflammation and edema in the brain. Similar to the ACS and leg ulcers, a significant reduction with hydroxyurea may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial inflammation and edema in the brain in the SCDs [44].

As a conclusion, SCDs are chronic inflammatory processes on vascular endothelium at the capillary level in whole body, and terminate with accelerated atherosclerosis induced end-organ failures including the heart failure in very early years of life.

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