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Atherosclerotic background of disseminated teeth losses in sickle cell diseases

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Abstract

Background: We tried to understand whether or not there is an atherosclerotic background of disseminated teeth losses in sickle cell diseases (SCDs). **Methods:** All patients with the SCDs were included, and cases with disseminated teeth losses (< 20 teeth present) were detected. **Results:** The study included 434 patients (222 males). Mean ages were similar in males and females (30.8 versus 30.3 years, respectively, P>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males (P<0.001 for both). Although the relatively younger mean ages, the prevalences of disseminated teeth losses were higher both in males and females (5.4% versus 1.4%, respectively, P<0.001). On the other hand, transfused units of red blood cells in their lives (48.1 versus 28.5, P=0.000), chronic obstructive pulmonary disease (25.2% versus 7.0%, P<0.001), ileus (7.2% versus 1.4%, P<0.001), cirrhosis (8.1% versus 1.8%, P<0.001), leg ulcers (19.3% versus 7.0%, P<0.001), digital clubbing (14.8% versus 6.6%, P<0.001), coronary artery disease (18.0% versus 13.2%, P<0.05), chronic renal disease (9.9% versus 6.1%, P<0.05), and stroke (12.1% versus 7.5%, P<0.05) were all higher in males. **Conclusion:** SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean ages of the study cases, the higher prevalences of disseminated teeth losses in both genders are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at arterial and venous systems of the oral mucosa, periodontium, and teeth in the SCDs.

Keywords: Sickle cell diseases, Chronic endothelial damage, Atherosclerosis, Disseminated teeth losses.

INTRODUCTION

Chronic endothelial damage may be the leading cause of aging and related morbidities and mortalities by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process because much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, 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 process are physical inactivity induced weight gain, smoking, alcohol, and other chronic infectious or inflammatory processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and related morbidities and mortalities. They were discussed under the title of metabolic syndrome in the literature, extensively [1,2]. Although early withdrawal of the causative factors may delay terminal endpoints, after development of obesity, HT, DM, PAD, COPD, cirrhosis, CRD, CAD, or stroke, the endothelial changes can not be reversed completely due to their fibrotic natures [3,4]. Similarly, disseminated teeth losses are also common health problems in elders, and they may also be found among the terminal consequences of the systemic atherosclerotic process. We tried to understand whether or not there is an atherosclerotic background of disseminated teeth losses in the SCDs.

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MATERİAL AND METHODS

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBCs) in their lives, surgical operations, leg ulcers, stroke, priapism, and lower urinary tract symptoms (LUTS) in males including urgency, weak stream, incomplete emptying, and nocturia were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Patients with disseminated teeth losses (< 20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and 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 BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bone was diagnosed by means of MRI [5]. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension [6]. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% [7]. An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. 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 findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign [8,9]. An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually prevalences of disseminated teeth losses were detected in both genders, and male and female patients with the SCDs were compared according to the terminal endpoints in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

RESULTS

The study included 434 patients with the SCDs (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, *P*>0.05). Prevalences of associated thalassemia minors were similar in males and females, too (72.5% versus 67.9%, respectively, *P*>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males (*P*<0.001 for both) (**Table 1**). Although the relatively younger mean ages of the patients, the prevalences of disseminated teeth losses were higher both in males and females (5.4% versus 1.4%, respectively, *P*<0.001). On the other hand, transfused units of RBCs in their lives (48.1 versus 28.5, *P*=0.000), COPD (25.2% versus 7.0%, *P*<0.001), ileus (7.2% versus 1.4%, *P*<0.001), cirrhosis (8.1% versus 1.8%, *P*<0.001), leg ulcers (19.8% versus 7.0%, *P*<0.001), digital clubbing (14.8% versus 6.6%, *P*<0.001), CAD (18.0% versus 13.2%, *P*<0.05), CRD (9.9% versus 6.1%, *P*<0.05), and stroke (12.1% versus 7.5%, *P*<0.05) were all higher in males, significantly (**Table 2**). There were 11 males (4.9%) with LUTS with a mean age of 41.5 ± 10.6 (27-58) years. All of the patients could be treated with once daily 4 milligrams of doxazosin, orally. Additionally, there were 23 cases (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were two cases with sickle cell retinopathy in males and two in females (0.9% versus 0.9%, *P*>0.05). There were 31 mortality cases (17 males and 14 females) during the ten-year period. The mean ages of mortality were 30.2 ± 8.4 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (*P*>0.05).

Table 1: Characteristic features of the study cases

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

*Sickle cell diseases †Nonsignificant (P>0.05)

DİSCUSSİON

SCDs are chronic inflammatory processes on vascular endothelium terminating 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 RBCs. Probably loss of elasticity instead of shape is the main pathology 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 damage, inflammation, and fibrosis terminate with disseminated cellular hypoxia all over the body [10,11]. As a difference from other etiologies of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level [12] because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage builds up a severe 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 [13], whereas they were 33.3 and 30.2 years in the present study, respectively. The big differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea, and inadequate RBC supports during emergencies in Turkey [14].

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCDs*	*P*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Disseminated teeth losses (< 20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
Transfused RBC‡ units	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
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)***
CAD¶	***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)***
Pulmonary hypertension	12.6% (28)	Ns	11.7% (25)
Varices	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)
Mortality	7.6% (17)	Ns	6.6% (14)

Sickle cell diseases †Nonsignificant (*P*>0.05) ‡Red blood cell §Chronic obstructive pulmonary diseases ¶Coronary artery disease **Chronic renal disease

Actually, RBC supports must be given immediately in all medical and surgical events in which there is an evidence of clinical deterioration in the SCDs [15]. RBC supports decrease sickle cell concentration in circulation and suppress bone marrow about the production of abnormal RBCs. So it decreases sickling-induced endothelial damage and inflammation all over the body.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the legs. Their related factors include pregnancy, menopause, obesity, aging, and heredity. In another word, varices are much more common in females and in cases with metabolic syndrome. Normally, leg muscles pump veins to return blood 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/or telangiectasias develop. Deep venous thrombosis may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, therefore physical examination should be performed in upright position in suspected cases. Although the much younger mean ages of the patients of the present study (30.8 years in males and 30.3 years in females) and significantly lower mean body mass index (BMI) of the SCDs cases in the literature [11], deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (9.0% in males and 6.6% in females, *P*>0.05) indicating an additional venous endothelial involvement in the SCDs.

Disseminated teeth losses are common health problems in elders, and there are several reports suggesting that oral and dental diseases are risk factors for cardiovascular diseases. Approximately 15% of population have severe periodontitis in England that is a chronic polymicrobial disease of the gums, and it may cause disseminated teeth losses [16]. Poor oral hygiene, periodontitis, and dental and pulpal caries lead to entry of bacteria into the blood stream and activation of the host immune system. The activated immune system may accelerate systemic atherosclerotic process. For example, there was a significant relationship between cardio-ankle vascular index and tooth loss in males [17]. Similarly, high levels of periodontal diseases were associated with high values of flow-mediated dilation of the brachial artery [18]. Additionally, the number of missing teeth was associated with intima-media thickness (IMT) of the carotid artery, and bleeding on probing was associated with IMT of the carotid artery in females [19]. Furthermore, significant associations were observed between hsCRP levels and dental status, oral hygiene, and IMT of the carotid and popliteal arteries [20]. Patients with increasing DMFT (number of decayed, missing, and filled teeth) and SLI (the Silness-Loe plaque index to evaluate oral hygiene and dental plaque) indexes correlated with increasing IMT of the carotid artery, and the authors concluded that poor oral hygiene and tooth loss are associated with subclinical atherosclerosis [21]. In another study, significant associations were detected between oral health status and COPD-related events, even adjusting for HT, DM, and smoking [22]. In another one, patients with less than one dental caries had a lower atherosclerotic burden, and the atherosclerotic burden was higher in patients with a higher number of lesions with pulpal involvement and more teeth with chronic apical periodontitis [23]. Eventually, age, number of dental caries, periodontitis, and male gender were found to be independent risk factors for atherosclerosis, and dental and pulpal caries and chronic apical periodontitis are associated with aortic atherosclerotic burden [23]. In longitudinal studies, excess risk of atherosclerotic cardiovascular disease was reported in patients with periodontitis, and limited evidence shows improvements in coagulation, biomarkers of endothelial cell activation, BP, and subclinical atherosclerosis after periodontal therapy [24]. In another study, there were significant associations between coronary atherosclerotic burden and age (>60 years), male gender, smoking, HT, DM, poor oral health, and disseminated teeth losses (< 20 teeth present) in the bivariate analysis [25]. The poor oral health and disseminated teeth losses were independently associated with coronary atherosclerotic burden in the multivariate models adjusted for age, gender, smoking, HT, DM, and dyslipidemia [25]. According to our clinical experiences, disseminated teeth losses may be indicators of general health status of the individuals. Although the poor oral hygiene, periodontitis, and dental and pulpal caries-induced low grade inflammation may cause a systemic accelerated atherosclerotic process, we actually think that they may be the consequences instead of the causes. Since aging, excess weight, smoking, alcohol, chronic infections and inflammations,

and cancers-induced systemic accelerated atherosclerotic process may strongly cause the above oral and dental pathologies by decreasing effective blood flow of the oral mucosa, periodontium, and teeth. Similarly, although the relatively younger mean age of the study cases (30.8 versus 30.3 years in males and females, respectively), the higher prevalences of disseminated teeth losses (5.4% versus 1.4% in males and females, respectively, *P*<0.001) are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at arterial and venous systems of the oral mucosa, periodontium, and teeth in the SCDs. Additionally, the disseminated teeth losses were higher in males similar to the literature [17,23,25] that may be secondary to the strong atherosclerotic effects of smoking and alcohol, since both of them were higher in males (*P*<0.001 for both) in the present study.

Both the frequency and complications of cirrhosis are increasing in the world. For example, it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 [4]. Although the achieved development of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by aging of the human being and increased frequency of excess weight in the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents, now [26,27]. NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process [26]. NAFLD shares many features of the metabolic syndrome. Beside terminating with cirrhosis, NAFLD is associated with a higher overall mortality as well as with an increased prevalence of cardiovascular diseases [27]. Authors have reported independent associations between NAFLD, impaired flow-mediated vasodilation, and increased IMT of the carotid artery [27,28]. NAFLD and cirrhosis may be considered as the hepatic consequences of the systemic accelerated atherosclerotic process, and hepatic fat is highly correlated with parameters of the metabolic syndrome [29]. Probably smoking is also important in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelium is already known with Buerger's disease and COPD [30]. Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic accelerated atherosclerotic process in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelial cells due to the much higher concentrations of its metabolites in the liver. Similarly, aging alone may be another cause of systemic atherosclerotic process that prevents adequate tissue oxygenation and tissue repair. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis [31]. For example, chronic HCV infection had raised IMT of the carotid artery, and normalisation of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the infection [31]. Similarly, beside the COPD, ileus, leg ulcers, digital clubbing, CAD, CRD, and stroke, cirrhosis may also be one of the terminal endpoints of the SCDs.

COPD is the third leading cause of mortality in the world [32]. It is an inflammatory disease mainly affecting the pulmonary vasculature. Physical inactivity induced weight gain, smoking, and aging may be the major underlying causes. Probably alcohol is also found in etiology of the inflammatory process. For example, both prevalences of alcohol and COPD were significantly higher in males in the present study (*P*<0.001 for both). Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study [33]. Additionally, 30-day readmission rates were higher in COPD patients with alcoholism [34]. 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 pulmonary losses. Although COPD is mainly be thought as an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of a systemic endothelial inflammation all over the body, and close relationships were observed between COPD, CAD, PAD, and stroke [35,36]. For example, 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 [37]. Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases in another study [38]. Eventually, due to the strong atherosclerotic backgrounds of COPD and SCDs, COPD may be one of the terminal endpoints of the SCDs [39].

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers [40]. 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 in the literature. Smoking induced endothelial damage is probably seen in pulmonary vasculature much more than the other organs due to the higher concentrations of its products, here. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products within the blood. On the other hand, beside the strong atherosclerotic effects, smoking in human being and nicotine in animals may be associated with some weight loss [41]. There may be an increased energy expenditure during smoking [42], and nicotine may decrease caloric intake in a dose-related manner [43]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten [44]. Similarly, BMI seems to be the highest in the former and the lowest in the current smokers [45]. 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 [46]. Eventually, although CAD was detected with similar prevalences in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its terminal consequences including dyslipidemia, HT, and DM in females [40]. Probably toxic substances of tobacco smoke cause a diffuse endothelial inflammation all over the body, and it is the major cause of loss of appetite during circulation of these substances within the blood, since body don't want to eat anything during fighting.

Digital clubbing is characterized by increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger [47]. Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine in the literature [9]. The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected [48]). In the above study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years [9]. But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and hepatic disorders those are featuring with chronic tissue hypoxia. As an explanation for that lungs, heart, and liver are closely related organs those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCDs and its prevalence was 10.8% in the present study. It may show chronic tissue hypoxia caused by disseminated endothelial inflammation at the capillary level in the SCDs. Beside the effects of SCDs, the higher prevalences of smoking, COPD, and clubbing in males (*P*<0.001 for all) may also show some additional roles of smoking, COPD, and male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs [49], and the ratio was 13.3% in the present study. Its incidence increases with age, male sex, and HbSS genotype [50]. Similarly, its ratio was higher in males (19.8% versus 7.0%, *P*<0.001), and mean age of the patients with leg ulcers was higher than the others (35.3 versus 29.8 years, *P*<0.000), here. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year [49]. As an evidence of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body [49]. The hard RBCs induced

chronic endothelial damage at the capillary level may be the major cause in the SCDs [50]. Prolonged exposure to the hard bodies due to blood pooling in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hard RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have effects on the developments of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have effects on the leg ulcers since both of them are more common in males. Hydroxyurea is the only drug that was approved by Food and Drug Administration for the treatment of SCDs [12]. 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 [14]. Its main action may be suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs [51]. Although presence of a continuous damage of hard RBCs on endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage [52]. According to our 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 at the capillary level in the SCDs.

CONCLUSIONS

As a conclusion, SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger means ages of the study cases, the higher prevalences of disseminated teeth losses in both genders are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at arterial and venous systems of the oral mucosa, periodontium, and teeth in the SCDs.

REFERENCES

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-1428.
2. Helvaci MR, Kaya H, Sevinc A, Camci C. Body weight and white coat hypertension. Pak J Med Sci 2009; 25: 6: 916-921.
3. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6: 3977-3981.
4. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52: 1-85.
5. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75: 274-283.
6. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179: 615-621.
7. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2010. Global initiative for chronic obstructive lung disease (GOLD).
8. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19: 325-329.
9. Schamroth L. Personal experience. S Afr Med J 1976; 50: 297-300.
10. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8: 11442-11448.
11. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27: 361-364.
12. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, *et al*. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312: 1033-1048.
13. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, *et al*. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330: 1639-1644.
14. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7: 2327-2332.
15. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1: 36-38.
16. Hussain M, Stover CM, Dupont A. P. gingivalis in Periodontal Disease and Atherosclerosis - Scenes of Action for Antimicrobial Peptides and Complement. Front Immunol 2015; 6: 45.
17. Asai K, Yamori M, Yamazaki T, Yamaguchi A, Takahashi K, Sekine A, *et al;* Nagahama Study Group. Tooth loss and atherosclerosis: the Nagahama Study. J Dent Res 2015; 94: 52-58.
18. Holtfreter B, Empen K, Gläser S, Lorbeer R, Völzke H, Ewert R, *et al*. Periodontitis is associated with endothelial dysfunction in a general population: a cross-sectional study. PLoS One 2013; 8: e84603.
19. Jung YS, Shin MH, Kim IS, Kweon SS, Lee YH, Kim OJ, *et al*. Relationship between periodontal disease and subclinical atherosclerosis: the Dong-gu study. J Clin Periodontol 2014; 41: 262-268.
20. Uyar IS, Akpinar MB, Sahin V, Yasa EF, Abacilar F, Yurtman V, *et al.* Carotid and popliteal artery intima-media thickness in patients with poor oral hygiene and the association with acute-phase reactants. Cardiovasc J Afr 2013; 24: 308-312.
21. Uyar IS, Sahin V, Akpinar MB, Abacilar F, Okur FF, Ozdemir U, *et al*. Does oral hygiene trigger carotid artery intima-media thickness? Heart Surg Forum 2013; 16: 232-236.
22. Barros SP, Suruki R, Loewy ZG, Beck JD, Offenbacher S. A cohort study of the impact of tooth loss and periodontal disease on respiratory events among COPD subjects: modulatory role of systemic biomarkers of inflammation. PLoS One 2013; 8: e68592.
23. Glodny B, Nasseri P, Crismani A, Schoenherr E, Luger AK, Bertl K, *et al*. The occurrence of dental caries is associated with atherosclerosis. Clinics (Sao Paulo) 2013; 68: 946-953.
24. Tonetti MS, Van Dyke TE; working group 1 of the joint EFP/AAP workshop. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013; 84: 24-29.
25. Gomes MS, Chagas P, Padilha DM, Caramori P, Hugo FN, Schwanke CH, *et al*. Association between self-reported oral health, tooth loss and atherosclerotic burden. Braz Oral Res 2012; 26: 436-442.
26. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33: 1190-1200.
27. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17: 3082-3091.
28. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69: 153-157.
29. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16: 1941-1951.
30. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28: 376-379.
31. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, *et al*. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59: 1135-1140.
32. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385: 1778-1788.
33. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. Eur Psychiatry 2015; 30: 459-468.
34. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. Chest 2016; 149: 905-915.
35. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, *et al*. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27: 627-643.
36. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 2000; 160: 2653-2658.
37. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166: 333-339.
38. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical

Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62: 411-415.
39. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7: 484-488.
40. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6: 3744-3749.
41. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, et al. National working conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. Health Psychol 1992; 11: 4-9.
42. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, Stamford BA. The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. Nicotine Tob Res 1999; 1: 365-370.
43. Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 1997; 9: 151-159.
44. Miyata G, Meguid MM, Varma M, Fetissov SO, Kim HJ. Nicotine alters the usual reciprocity between meal size and meal number in female rat. Physiol Behav 2001; 74: 169-176.
45. Laaksonen M, Rahkonen O, Prattala R. Smoking status and relative weight by educational level in Finland, 1978-1995. Prev Med 1998; 27: 431-437.
46. Helvaci MR, Kaya H, Gundogdu M. Association of increased triglyceride levels in metabolic syndrome with coronary artery disease. Pak J Med Sci 2010; 26: 667-672.
47. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286: 341-347.
48. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75: 511-513.
49. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17; 410-416.
50. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85: 831-833.
51. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. Pren Med Argent 2014; 100: 49-56.
52. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34: 15-21..