Int J Clin Exp Med 2016;9(6):11950-11957
www.ijcem.com /ISSN:1940-5901/IJCEM0023139

Original Article

Venous involvement in sickle cell diseases

Mehmet Rami Helvaci[1], Cumali Gokce[1], Mustafa Sahan[2], Sedat Hakimoglu[3], Mesut Coskun[4], Kerem Han Gozukara[5]

Departments of [1]Internal Medicine, [2]Emergency Medicine, [3]Anesthesiology and Reanimation, [4]Ophthalmology, [5]Urology, Medical Faculty of Mustafa Kemal University, Mustafa Kemal University, Serinyol, Antakya, Hatay, Turkey

Received January 3, 2016; Accepted May 5, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Background: Sickle cell diseases (SCDs) cause an accelerated atherosclerotic process in whole body. We tried to understand whether or not there is an additional venous involvement in the SCDs. Methods: As one of the significant endpoints of the SCDs, cases with chronic obstructive pulmonary disease (COPD) and without were collected into the two groups. Results: The study included 427 patients (220 males). There were 71 patients (16.6%) with COPD. Mean age of patients was significantly higher in the COPD group (32.8 versus 29.8 years, P=0.005). The male ratio was significantly higher in the COPD group, too (78.8% versus 46.0%, P<0.001). Smoking (35.2% versus 11.2%, P<0.001) and alcohol (7.0% versus 1.9%, P<0.01) were also higher among the COPD cases. Beside these, priapism (14.0% versus 2.8%, P<0.001), cirrhosis (8.4% versus 3.3%, P<0.05), leg ulcers (23.9% versus 12.0%, P<0.01), digital clubbing (25.3% versus 6.7%, P<0.001), coronary heart disease (23.9% versus 13.7%, P<0.05), chronic renal disease (15.4% versus 7.0%, P<0.01), and stroke (16.9% versus 8.1%, P<0.01) were all higher among the COPD cases. Although deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were also higher among them, the difference was nonsignificant (11.2% versus 5.0%, P>0.05) probably due to small sample size of the COPD group. Conclusion: SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Beside the accelerated atherosclerotic process, venous involvement may also be common in the SCDs.

Keywords: Sickle cell diseases, chronic endothelial damage, deep venous thrombosis, varice, telangiectasia

Introduction

Chronic endothelial damage may be the major cause of aging and mortality by inducing generalized hypoxia in body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are mainly involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, weight gain, smoking, and alcohol for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively [1, 2]. Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on vascular endothelium particularly 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 because sickling is rare in peripheric blood samples of patients with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced prolonged endothelial inflammation, edema, and fibrosis mainly at the capillary level terminate with hypoxia in whole body [3-5]. Capillary vessels are mainly involved in the process due to their distribution function for the hard bodies. Beside the accelerated atherosclerotic process, we tried to understand

Table 1. Characteristic features of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Prevalence	16.6% (71)		83.3% (356)
Male ratio	*78.8% (56)*	*<0.001*	*46.0% (164)*
Mean age (year)	*32.8 ± 10.0 (5-58)*	*0.005*	*29.8 ± 9.9 (6-59)*
Thalassemia minors	76.0% (54)	Ns†	68.5% (244)
Smoking	*35.2% (25)*	*<0.001*	*11.2% (40)*
Alcoholism	*7.0% (5)*	*<0.01*	*1.9% (7)*

*Chronic obstructive pulmonary disease, †Nonsignificant (*P*>0.05).

whether or not there is an additional venous involvement in the SCDs in the present study.

Material and methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and January 2016. The study included 427 patients with the SCDs (207 females and 220 males) without any exclusion criterion during the nine-year period. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units in their lives, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same physician. Cases with acute painful crisis or another inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C 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 was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia [6]. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% during the silent phase [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. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension [8]. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination, hepatic function tests, ultrasonographic results, and tissue sample in case of indication. 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 [9, 10]. An exercise electrocardiogram is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Avascular necrosis of bones is diagnosed by means of MRI [11]. Stroke is diagnosed by the computed tomography of brain. Ophthalmologic examination was performed according to the patients' complaints. Eventually as one of the significant endpoints of the SCDs, cases with COPD and without were collected into the two groups, and the groups were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

There were 71 patients (16.6%) with COPD. Mean age of the patients was significantly higher in the COPD group (32.8 versus 29.8 years,

Table 2. Associated pathologies of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Painful crises per year	5.3 ± 7.9 (0-36)	Ns†	4.9 ± 7.9 (0-52)
Transfused RBC‡ units	*63.8 ± 85.1 (0-434)*	*0.003*	*33.1 ± 39.7 (0-250)*
Priapism	*14.0% (10)*	*<0.001*	*2.8% (10)*
Ileus	4.2% (3)	Ns	3.3% (12)
Cirrhosis	*8.4% (6)*	*<0.05*	*3.3% (12)*
Leg ulcers	*23.9% (17)*	*<0.01*	*12.0% (43)*
Pulmonary hypertension	12.6% (9)	Ns	12.0% (43)
Varices	11.2% (8)	Ns	5.0% (18)
Digital clubbing	*25.3% (18)*	*<0.001*	*6.7% (24)*
CHD§	*23.9% (17)*	*<0.05*	*13.7% (49)*
CRD¶	*15.4% (11)*	*<0.01*	*7.0% (25)*
Rheumatic heart disease	7.0% (5)	Ns	6.1% (22)
Avascular necrosis of bones	21.1% (15)	Ns	25.2% (90)
ACS**	1.4% (1)	Ns	3.6% (13)
Stroke	*16.9% (12)*	*<0.01*	*8.1% (29)*
Mortality	7.0% (5)	Ns	6.4% (23)

*Chronic obstructive pulmonary disease, †Nonsignificant (*P*>0.05), ‡Red blood cell, §Coronary heart disease, ¶Chronic renal disease, **Acute chest syndrome.

P=0.005). The male ratio was significantly higher in the COPD group, too (78.8% versus 46.0%, *P*<0.001). Smoking (35.2% versus 11.2%, *P*< 0.001) and alcohol consumption (7.0% versus 1.9%, *P*<0.01) were also higher among the COPD cases. Prevalences of associated thalassemia minors were similar in both groups (76.0% versus 68.5% in the COPD group and other, respectively, *P*>0.05) (**Table 1**). Beside these, transfused RBC units in their lives (63.8 versus 33.1, *P*=0.003), priapism (14.0% versus 2.8%, *P*<0.001), cirrhosis (8.4% versus 3.3%, *P*<0.05), leg ulcers (23.9% versus 12.0%, *P*< 0.01), digital clubbing (25.3% versus 6.7%, *P*<0.001), CHD (23.9% versus 13.7%, *P*<0.05), CRD (15.4% versus 7.0%, *P*<0.01), and stroke (16.9% versus 8.1%, *P*<0.01) were all higher among the COPD cases. Although deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were also higher, the difference was nonsignificant (11.2% versus 5.0%, *P*>0.05) probably due to the small sample size of the COPD group (**Table 2**). There were 28 mortality (15 males) during the nine-year period. The mean ages of mortality were 33.6 ± 9.5 years (range 19-47) in females and 30.8 ± 8.6 years (range 19-50) in males (*P*>0.05). On the other hand, there were three patients with sickle cell retinopathy, all of them were found in cases without the COPD. Additionally, there were five patients with HBsAg positivity (1.1%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR). Although antiHCV was positive in 5.8% (25) of the study cases, HCV RNA was detected as positive just in four (0.9%) by PCR.

Discussion

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of aging and mortality in human being. Physical inactivity, weight gain, smoking, alcohol, prolonged infections, and chronic inflammatory processes including SCDs, rheumatologic disorders, and cancers may accelerate the process. Probably whole afferent vasculature including capillaries are mainly involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent micro-injuries on endothelium. Therefore the term of venosclerosis is not as famous as arteriosclerosis or 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 BP further. Although early withdrawal of causative factors may delay final consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, endothelial changes can not be reversed due to the fibrotic natures of them [12].

SCDs are life-threatening hereditary disorders affecting nearly 100,000 individuals in the United States [13]. As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level [14], since the capillary system is the main distributor of the hard RBCs to the tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced

atherosclerosis in 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 [15], whereas they were 33.6 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed diagnosis of the diseases, delayed initiation of hydroxyurea therapy, and inadequate RBC supports in crises in our country. Actually, RBC support must be given whenever there is an evidence of clinical deterioration in the SCDs [16, 17]. RBC support decreases sickle cell concentration in circulation and suppresses bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage on organs in crises. According to our nine-year experiences, simple transfusions are superior to RBC exchange. First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or more gives time to clinicians to prepare more units by preventing sudden death of such 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 families in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of simple transfusions will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange. On the other hand, longer lifespan of females in the SCDs [15] and longer overall survival of females in the world [18] can not be explained by the atherosclerotic effects of smoking or alcohol alone, instead it may be explained by physical power requiring role of male sex in life that may terminate with an exaggerated sickling and atherosclerosis in the body [19].

COPD is the third leading cause of mortality with different causative factors in the world [20]. It is an inflammatory disorder mainly affecting the pulmonary vasculature, and smoking, excess weight, and aging may be the major causes. Regular alcohol consumption may also take place in the inflammatory process. For example, the prevalence of alcohol consumption was significantly higher in the COPD group in the present study (7.0% versus 1.9%, $P<0.01$). Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study [21]. Additionally, 30-day readmission rate was higher in COPD patients with alcoholism [22]. Probably the accelerated atherosclerotic process is the main structural background of functional changes that are characteristics 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 lungs. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of generalized endothelial inflammation in whole body [23, 24]. For example, close relationships were shown between COPD, CHD, PAD, and stroke [25]. Similarly, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in smokers in a multi-center study [26]. When the hospitalizations were researched, the most common causes were the cardiovascular diseases again [26]. In another study, 27% of all mortality were due to the cardiovascular causes in the moderate and severe COPD cases [27]. Due to the strong atherosclerotic natures of the SCDs and COPD, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalences of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the COPD group [28].

Smoking may have major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers [12, 29]. Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease is an inflammatory process terminating with obliterative changes in blood vessels, and it has never been reported in the absence of smoking. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products, here. But smoking may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers by the transport within the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. On the other hand, beside the strong atherosclerotic effects, smoking in human being and nicotine administration in animals may be associated with some weight loss [30]. There may be an increased energy expenditure during smoking [31], and nicotine

may decrease caloric intake in a dose-related manner [32]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten [33]. Similarly, body mass index (BMI) seems to be the highest in former, the lowest in current, and medium in never smokers [34]. 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 [35]. Additionally, although CHD were 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 [29]. Probably toxic substances of tobacco smoke cause an acute inflammation on vascular endothelium in whole body, and it is the major cause of loss of appetite during circulation of the substances within blood, since body can't eat anything during fighting. On the other hand, when we thought some antidepressant properties of smoking and alcohol, the higher prevalences of them may also show some additional stresses and shorthened survival in male sex in life.

Digital clubbing may help to identify some systemic disorders in the body. 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 [36]. Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine [9], whereas the prevalence was 4.2% in the same department in our university [12]. The exact cause and significance is unknown but chronic tissue hypoxia has been proposed [37, 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 [9]. But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, and/or hepatic disorders or smoking that are featuring with chronic tissue hypoxia. As an explanation for that lungs, heart, and liver are closely related organs that affect their functions in a short period of time. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis particularly at the capillary level in the SCDs, and we observed clubbing in 9.8% of patients with the SCDs in the present study. Beside the effects of SCDs, the higher prevalences of smoking (35.2% versus 11.2%, $P<0.001$) and clubbing (25.3% versus 6.7%, $P<0.001$) in the COPD group may also show some additional roles of smoking and COPD on digital clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs [39], and the ratio was 14.0% in the present study. Its incidence increases with age, male sex, and HbSS genotype [39]. Similarly, its ratio was 20.4% in males and 7.2% in females in the present study ($P<0.001$). Beside that, mean age of the patients with leg ulcers was higher than the patients without (34.8 versus 29.5 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 [40]. As an evidence of their atherosclerotic background, the leg ulcers occur in distal areas with less collaterally blood flow in the body [40]. The hard RBCs induced chronic endothelial damage particularly at the capillary level may be the major cause in the SCDs [39]. 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 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 nine-year experiences, prolonged resolution of leg ulcers with hydroxyurea therapy may also suggest that they may be secondary to increased WBC and PLT counts induced prolonged endothelial inflammation and edema in the SCDs.

Stroke is also a frequent complication of the SCDs [41]. Similar to the ACS and leg ulcers, it is more common with the HbSS genotype and a higher WBC count [42, 43]. Sickling induced generalized endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain [44]. Stroke may not have a

macrovascular origin, instead generalized endothelial inflammation and edema, particularly at the capillary level, may be much more important in the SCDs. Infections, inflammations, and various stresses may precipitate the stroke because increased metabolic rate during such events may precipitate sickling and secondary endothelial inflammation and edema. Similar to the ACS and leg ulcers, a significant reduction with hydroxyurea therapy may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced generalized endothelial inflammation and edema in the SCDs [14, 45].

Varices are abnormally dilated vessels with tortuous courses. They usually occur in the venous system of the legs. Related factors include pregnancy, obesity, menopause, aging, and heredity. In another word, varices are more common in females. Interestingly, deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher in males in the present study (7.7% versus 4.3%, $P<0.05$). Some proportion of the difference may be due to endothelial toxicities of smoking and alcohol, since both of them were significantly higher in males, here (23.6% versus 6.2% in smoking and 5.0% versus 0.4% in alcohol, $P<0.001$ for both). Normally, leg muscles pump veins to return blood to the heart 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. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Deep venous thrombosis is another possible cause of varicose veins. Severe long-standing varicose veins can lead to leg swelling, venous eczema, skin thickening, and ulcerations, but life-threatening complications are rare. Because most of blood in the legs is returned by deep veins and superficial veins return only about 10% of total blood, varices can usually be removed without serious harm, surgically. Although the young mean age of the study cases (30.3 years) here, the high prevalences of deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs (6.0%) may show an additional venous involvement in the SCDs.

Priapism is the painful erection of penis which does not return to its flaccid state within four hours in the absence of any stimulation [46]. It is an emergency since damage to the blood vessels may terminate with fibrosis of the corpus cavernosa and eventually a shortened, indurated, and non-erectile penis [46]. Ischemic (veno-occlusive), recurrent ischemic, and non-ischemic ones (arterial) are the three types of priapism [47]. Ninety-five percent of clinically presented priapisms are ischemic or veno-occlusive types in which blood can not return adequately from the penis to body as in the SCDs [46, 47]. The remaining 5% are nonischemic or arterial types that usually caused by a blunt perineal trauma in which there is a short-circuit of the vascular system in the penis [46]. Treatment of arterial type is not as urgent as that of venous type since there is no risk of ischemia [46]. Due to the highly suspected venous nature of priapism in the SCDs, the high prevalence of priapism (4.6%) in the present study may also show an additional venous involvement in the SCDs.

As a conclusion, SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Beside the accelerated atherosclerotic process, venous involvement may also be common in the SCDs.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mehmet Rami Helvaci, Departments of Internal Medicine, Medical Faculty of the Mustafa Kemal University, Serinyol, Antakya 31100, Hatay, Turkey. Tel: 00-90-326-22-91000; Fax: 00-90-326-2455654; E-mail: mramihelvaci@hotmail.com

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, Gokce C, Davran R, Acipayam C, Akkucuk S, Ugur M. Tonsilectomy in sickle cell diseases. Int J Clin Exp Med 2015; 8: 4586-4590.

[4] 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.
[5] Helvaci MR, Gokce C, Davarci M, Sahan M, Hakimoglu S, Coskun M. Chronic endothelial inflammation and priapism in sickle cell diseases. Int J Clin Exp Med 2016; (in press).
[6] Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, Vera JC, Levy PS. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood 1994; 84: 643-649.
[7] Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2010. Global initiative for chronic obstructive lung disease (GOLD).
[8] Fisher MR, Forfia PR, Chamera E, Houston-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179: 615-621.
[9] 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.
[10] Schamroth L. Personal experience. S Afr Med J 1976; 50: 297-300.
[11] Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, Shah A, Yang YM, Brogdon BG. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75: 274-283.
[12] Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. Health Med 2012; 6: 3977-3981.
[13] Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, Jordan L, Lanzkron SM, Lottenberg R, Savage WJ, Tanabe PJ, Ware RE, Murad MH, Goldsmith JC, Ortiz E, Fulwood R, Horton A, John-Sowah J. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312: 1033-1048.
[14] Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. Health Med 2013; 7: 2327-2332.
[15] Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330: 1639-1644.
[16] Charache S, Scott JC, Charache P. "Acute chest syndrome" in adults with sickle cell anemia. Microbiology, treatment, and prevention. Arch Intern Med 1979; 139: 67-69.
[17] Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1: 36-38.
[18] Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD. Healthy life expectancy in 191 countries, 1999. Lancet 2001; 357: 1685-1691.
[19] Helvaci MR, Ayyildiz O, Gundogdu M. Gender differences in severity of sickle cell diseases in non-smokers. Pak J Med Sci 2013; 29: 1050-1054.
[20] Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385: 1778-1788.
[21] 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.
[22] 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.
[23] Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279: 1477-1482.
[24] Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, Davey Smith G, Upton M, Hawthorne V, Sin DD, Man SF, Van Eeden S, Mapel DW, Vestbo J. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27: 627-643.
[25] 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.
[26] 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.
[27] 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.
[28] Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. Health Med 2013; 7: 484-488.
[29] Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. Health Med 2012; 6: 3744-3749.

[30] Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, O'Connell K, Pomerleau OF, Ravussin E, Rolls BJ. 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.
[31] 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.
[32] 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.
[33] 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.
[34] Laaksonen M, Rahkonen O, Prattala R. Smoking status and relative weight by educational level in Finland, 1978-1995. Prev Med 1998; 27: 431-437.
[35] 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.
[36] Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286: 341-347.
[37] Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75: 511-513.
[38] Fomin VV, Popova EN, Burnevich EZ, Kuznetsova AV. Hippocratic fingers: clinical importance and differential diagnosis. Klin Med (Mosk) 2007; 85: 64-68.
[39] Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85: 831-833.
[40] Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004; 17: 410-416.
[41] Gueguen A, Mahevas M, Nzouakou R, Hosseini H, Habibi A, Bachir D, Brugière P, Lionnet F, Ribei JA, Godeau B, Girot R, Ibrahima V, Calvet D, Galactéros F, Bartolucci P. Sickle-cell disease stroke throughout life: a retrospective study in an adult referral center. Am J Hematol 2014; 89: 267-272.
[42] Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, Megason G, Iyer R. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. Br J Haematol 2014; 165: 707-713.
[43] 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.
[44] Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21: 404-414.
[45] Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332: 1317-1322.
[46] Kaminsky A, Sperling H. Diagnosis and management of priapism. Urologe A 2015; 54: 654-661.
[47] Broderick GA. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. J Sex Med 2012; 9: 88-103.