Atherosclerotic background of hepatosteatosis in sickle cell diseases

Mehmet Rami Helvaci (1)
Mustafa Yaprak (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Specialist of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD
(3) medi+WORLD International

Corresponding authr:
Mehmet Rami Helvaci, MD
07400, ALANYA,
Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Received: January 30, 2018; Accepted: February 10, 2018; Published: March 1, 2018
Citation: Helvaci M. et al. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Medicine. 2018; 16(3):12-18. DOI: 10.5742/MEWFM.2018.93305

Abstract

Background: We tried to understand whether or not there is an atherosclerotic background of hepatosteatosis in sickle cell diseases (SCDs).

Methods: All male and female patients with the SCDs were studied.

Results: The study included 428 patients (208 females). The mean ages of patients were similar in males and females (30.6 versus 30.1 years, respectively, P>0.05). Smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males (P<0.001 for both). Although the inflammatory nature induced severe weight loss of the SCDs and relatively younger mean ages of the patients, there were nine (4.0%) hepatosteatosis cases in males and six (2.8%) in females (P>0.05). Their mean ages were 37.5 years in males and 31.8 years in females (P>0.05). Their mean body mass indexes were 25.8 kg/m2 in males and 23.2 kg/m2 in females (P>0.05). On the other hand, transfused red blood cell units in their lives (47.6 versus 28.4, P=0.000), chronic obstructive pulmonary disease (25.4% versus 7.2%, P<0.001), ileus (7.2% versus 1.4%, P<0.001), cirrhosis (7.2% versus 1.9%, P<0.001), leg ulcers (20.0% versus 7.2%, P<0.001), digital clubbing (14.0% versus 6.2%, P<0.001), coronary artery disease (18.1% versus 12.9%, P<0.05), chronic renal disease (10.4% versus 6.2%, P<0.05), and stroke (12.2% versus 7.6%, P<0.05) were all higher in males.

Conclusion: 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. Hepatosteatosis may actually be one of the hepatic consequences of accelerated atherosclerotic process in the SCDs.

Key words: Sickle cell diseases,
chronic endothelial damage, atherosclerosis,
hepatosteatosis

Introduction

Chronic endothelial damage may be the major cause of aging, morbidity, and mortality by causing disseminated tissue hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity induced weight excess, smoking, and alcohol consumption 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. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). 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 because 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 life, 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 (3, 4). Capillary vessels are mainly involved in the process due to their distribution function for the hard bodies. We tried to understand whether or not there is an atherosclerotic background of hepatosteatosis in the SCDs in the present study.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with 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, leg ulcers, and stroke 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. 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, 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. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (5). 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 (6). 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, liver function tests, ultrasonographic evaluation, and tissue samples in case of indication. Hepatosteatosis is diagnosed, ultrasonographically. 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 (7, 8). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just 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. Avascular necrosis of bones is diagnosed by means of MRI (9). Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually male and female patients were collected into the two groups, and compared 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 428 patients with the SCDs (208 females and 220 males). Mean ages of the patients were similar in males and females (30.6 versus 30.1 years, respectively, $P>0.05$). Prevalence of associated thalassemia minors were similar in males and females, too (72.2% versus 67.7%, respectively, $P>0.05$). Smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males ($P<0.001$ for both) (Table 1). Although the inflammatory nature induced severe weight loss of the SCDs and relatively younger mean ages of the patients, there were nine (4.0%) hepatosteatosis cases in males and six (2.8%) in females ($P>0.05$). Their mean ages were 37.5 years in males and 31.8 years in females ($P>0.05$). Their mean body mass indexes (BMI) were 25.8

Table 1: Characteristic features of the study cases

Variables	Male patients with SCDs*	*P*-value	Female patients with SCDs
Prevalence	51.4% (220)	Ns†	48.5% (208)
Mean age (year)	30.6 ± 10.1 (5-58)	Ns	30.1 ± 9.9 (8-59)
Thalassemia minors	72.2% (159)	Ns	67.7% (141)
Smoking	***24.0% (53)***	***<0.001***	***6.2% (13)***
Alcoholism	***5.0% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (P>0.05)

Table 2: Clinical features of the hepatosteatosis cases

Variables	Male patients with SCDs*	*P*-value	Female patients with SCDs
Prevalence of hepatosteatosis	4.0% (9)	Ns†	2.8% (6)
Mean age of hepatosteatosis (year) cases	37.5 ± 10.5 (23-58)	Ns	31.8 ± 9.6 (22-47)
Mean BMI‡ of hepatosteatosis (kg/m2) cases	25.8 ± 3.2 (21.4-32.5)	Ns	23.2 ± 1.5 (20.8-25.2)

*Sickle cell diseases †Nonsignificant (P>0.05) ‡Body mass index

Table 3: 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)
Transfused RBC‡ units	***47.6 ± 61.6 (0-434)***	***0.000***	***28.4 ± 35.8 (0-206)***
COPD§	***25.4% (56)***	***<0.001***	***7.2% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***7.2% (16)***	***<0.001***	***1.9% (4)***
Leg ulcers	***20.0% (44)***	***<0.001***	***7.2% (15)***
Digital clubbing	***14.0% (31)***	***<0.001***	***6.2% (13)***
CAD¶	***18.1% (40)***	***<0.05***	***12.9% (27)***
CRD*	***10.4% (23)***	***<0.05***	***6.2% (13)***
Stroke	***12.2% (27)***	***<0.05***	***7.6% (16)***
Pulmonary hypertension	12.7% (28)	Ns	12.5% (26)
Varices	8.6% (19)	Ns	5.7% (12)
Rheumatic heart disease	6.8% (15)	Ns	5.7% (12)
Avascular necrosis of bones	25.0% (55)	Ns	25.0% (52)
Sickle cell retinopathy	0.9% (2)	Ns	0.4% (1)
Mortality	7.2% (16)	Ns	6.7% (14)

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

kg/m2 in males and 23.2 kg/m2 in females (P>0.05) (Table 2). On the other hand, transfused RBC units in their lives (47.6 versus 28.4, P=0.000), COPD (25.4% versus 7.2%, P<0.001), ileus (7.2% versus 1.4%, P<0.001), cirrhosis (7.2% versus 1.9%, P<0.001), leg ulcers (20.0% versus 7.2%, P<0.001), digital clubbing (14.0% versus 6.2%, P<0.001), CAD (18.1% versus 12.9%, P<0.05), CRD (10.4% versus 6.2%, P<0.05), and stroke (12.2% versus 7.6%, P<0.05) were all higher in males, significantly. There were two cases with sickle cell retinopathy in males and one in females (P>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period. The mean ages of mortality were 30.8 ± 8.3 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (P>0.05) (Table 3). Beside these, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV was positive in 5.8% (25) of the study cases, HCV RNA was detected as positive just in three (0.7%) by PCR.

Discussion

Chronic endothelial damage, as the most common type of vasculitis, may be the leading cause of aging, morbidity, and mortality in human beings. Physical inactivity induced weight excess, smoking, alcohol consumption, and chronic inflammatory processes including SCDs, rheumatologic disorders, prolonged infections, 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 injuries on endothelium. 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. Although early withdrawal of causative factors may prevent final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature (10).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (11). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium at the capillary level (12), 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 and 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 (13), whereas they were 33.3 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 support during severe medical or surgical events in Antakya region. Actually, RBC support must be given during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (14, 15). 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 all over the body during such events. According to our ten-year experiences, simple RBC transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions at each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBC suspensions at 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 at each time 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 (13) and longer overall survival of females in the world (16) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by higher physical and emotional stresses of male sex in life that may terminate with an exaggerated sickling and atherosclerosis all over the body (17).

Excessive fat accumulation in hepatocytes is called as hepatosteatosis. It is usually accepted as one of the hepatic manifestations of metabolic syndrome. It progresses 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 (18). Hepatosteatosis may actually be one of the consequences of chronic inflammatory processes including physical inactivity induced weight excess, smoking, alcohol consumption, infections, cancers, and other inflammatory disorders, and is strongly associated with an accelerated atherosclerotic process not only in the liver, butall over the body. For example, hepatosteatosis is seen in one-third of cases with hepatitis B virus-related chronic liver disease (19). Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas (20). The liver density measurement on contrast abdominopelvic computed tomography of colorectal cancer cases was low, which is consistent with NAFLD in another study (21). As an acute phase reactant, serum thrombopoietin levels increased in patients with NAFLD (22). 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 in another study (23). 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 (24). Furthermore, patients with NAFLD have more complex CAD (25). 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) (26). Similarly, NAFLD was correlated with the severity of CAD and CIMT in another study ($P<0.001$ for both) (27). 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 (28). Additionally, degree of hepatosteatosis was correlated with the right ventricular diastolic dysfunction (29). According to our opinion, hepatosteatosis may actually be one of hepatic consequences of the systemic atherosclerotic process in the SCDs.

COPD is the third leading cause of mortality in the world (30). 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. For example, both prevalence of alcohol consumption 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 (31). Additionally, 30-day readmission rate to the hospitals was higher in COPD patients with alcoholism (32). Probably caused by 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 loss in the lungs. Although COPD may mainly be thought of 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 (33, 34). Two-thirds 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 in another study (35). Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases (36). Due to the strong atherosclerotic nature of the SCDs and COPD, COPD maybe one of the terminal consequences of the SCDs is due to the higher prevalences of priapism, leg ulcers, digital clubbing, CAD, CRD, and stroke in the COPD group in another study (37).

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers (38). 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 concentration of its products, there. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products 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 beings and nicotine in animals may be associated with some weight loss (39). There may be an increased energy expenditure during smoking (40), and nicotine may decrease caloric intake in a dose-related manner (41). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (42). Similarly, BMI seems to be the highest in the former and the lowest in the current smokers (43). 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 (44). Additionally, although CAD was detected with similar prevalence 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 (38). Probably toxic substances of tobacco smoke cause a diffuse inflammation on vascular endothelium all over the body, and it is the major cause of loss of appetite during circulation of the substances within the blood, since the body can't eat anything during fighting. So regular smoking comes with a prominent weight loss in front of us, clinically. On the other hand, when we thought of some antidepressant properties of smoking and alcohol consumption, the higher prevalences of them in males may also show some additional stresses and shorthened survival in them.

Digital clubbing should alert physicians about some systemic disorders in the body (10). 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 (45). Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine (7), whereas the prevalence was 4.2% in the same department in our university (10). The exact cause and significance is unknown but chronic tissue hypoxia has been proposed (46). In the above study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (7). But 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. 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 at the capillary level in the SCDs, and we observed clubbing in 10.2% of patients with the SCDs in the present study. 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 (47), and the ratio was 13.7% in the present study. Its incidence increases with age, male sex, and HbSS genotype (47). Similarly, its ratio was higher in males (20.0% versus 7.2%, $P<0.001$), and mean age of the patients with leg ulcers was higher than the others (35.1 versus 29.6 years, $P<0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (48). As an evidence of their atherosclerotic background, the leg ulcers occur in distal areas with less collateral blood flow in the body (48). The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause in the SCDs (47). 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 COPD, Buerger's disease, and cirrhosis (47). According to our ten-year experience, 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 (49). Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count (50, 51). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (51). 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, inflammatory disorders, and other 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 (52).

As a conclusion, 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. Hepatosteatosis may actually be one of the hepatic consequences of accelerated atherosclerotic process 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, 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.
4. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27: 361-364.
5. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2010. Global initiative for chronic obstructive lung disease (GOLD).
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. 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.
8. Schamroth L. Personal experience. S Afr Med J 1976; 50: 297-300.
9. 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.
10. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6: 3977-3981.
11. 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.
12. 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.
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. 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.
15. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1: 36-38.
16. Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD. Healthy life expectancy in 191 countries, 1999. Lancet 2001; 357: 1685-1691.
17. 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.
18. Sun Z, Lazar MA. Dissociating fatty liver and diabetes. Trends Endocrinol Metab 2013; 24: 4-12.
19. Rastogi A, Sakhuja P, Kumar A, Hissar S, Jain A, Gondal R, et al. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. Indian J Pathol Microbiol 2011; 54: 454-459.
20. Köse D, Erol C, Kaya F, Koplay M, Köksal Y. Development of fatty liver in children with non-Hodgkin lymphoma. Turk J Pediatr 2014; 56: 399-403.
21. Aktas E, Uzman M, Yildirim O, Sahin B, Buyukcam F, Aktas B, et al. Assessment of hepatic steatosis on contrast enhanced computed tomography in patients with colorectal cancer. Int J Clin Exp Med 2014; 7: 4342-4346.
22. Balcik OS, Akdeniz D, Cipil H, Ikizek M, Uysal S, Kosar A, et al. Serum thrombopoietin levels in patients with non-alcoholic fatty liver disease. Saudi Med J 2012; 33: 30-33.
23. Çiftci A, Yilmaz B, Köklü S, Yüksel O, Özsoy M, Erden G, et al. Serum levels of nitrate, nitrite and advanced oxidation protein products (AOPP) in patients with nonalcoholic fatty liver disease. Acta Gastroenterol Belg 2015; 78: 201-205.
24. Kucukazman M, Ata N, Yavuz B, Dal K, Sen O, Deveci OS, et al. Evaluation of early atherosclerosis markers in patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2013; 25: 147-51.
25. Agaç MT, Korkmaz L, Cavusoglu G, Karadeniz AG, Agaç S, Bektas H, et al. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. Angiology 2013; 64: 604-608.
26. Inci MF, Özkan F, Ark B, Vurdem ÜE, Ege MR, Sincer I, et al. Sonographic evaluation for predicting the presence and severity of coronary artery disease. Ultrasound Q 2013; 29: 125-130.
27. Öztürk H, Gümrükçüoğlu HA, Yaman M, Akyol A, Öztürk Ş, Akdağ S, et al. Hepatosteatosis and carotid intima-

-media thickness in patients with myocardial infarction. J Med Ultrason (2001) 2016; 43: 77-82.
28. Karasin M, Tokgoz O, Serifoglu I, Oz I, Erdem O. The Doppler ultrasonographic evaluation of hemodynamic changes in hepatic vascular structures in patients with hepatosteatosis. Pol J Radiol 2014; 79: 299-304.
29. Bekler A, Gazi E, Erbag G, Binnetoglu E, Barutcu A, Sen H, et al. Right ventricular function and its relationship with grade of hepatosteatosis in non-alcoholic fatty liver disease. Cardiovasc J Afr 2015; 26: 109-113.
30. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385: 1778-1788.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7: 484-488.
38. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6: 3744-3749.
39. 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.
40. 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.
41. 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.
42. 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.
43. Laaksonen M, Rahkonen O, Prattala R. Smoking status and relative weight by educational level in Finland, 1978-1995. Prev Med 1998; 27: 431-437.
44. 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.
45. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286: 341-347.
46. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75: 511-513.
47. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85: 831-833.
48. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17; 410-416.
49. Gueguen A, Mahevas M, Nzouakou R, Hosseini H, Habibi A, Bachir D, et al. Sickle-cell disease stroke throughout life: a retrospective study in an adult referral center. Am J Hematol 2014; 89: 267-272.
50. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. Br J Haematol 2014; 165: 707-713.
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, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. 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.