# What a high prevalence of rheumatic heart disease in sickle cell patients

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## Abstract

Background: We tried to understand whether or not there is a higher prevalence of rheumatic heart disease (RHD) in the sickle cell diseases (SCDs).
Methods: All patients with the SCDs and controls were studied.

Results: The study included 428 patients with the SCDs (208 females) and 2,855 controls (1,620 females). Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Mean ages of the controls were 40.8 versus 41.8 years, respectively (p<0.001 for both). Although the higher mean ages and female predominance (56.7% versus 48.5%, p<0.001) of the control cases, RHD was detected just in 0.3% of them (eight females and one male). Whereas this ratio was 6.5% (13 females and 15 males) in the SCDs (p<0.001). The mean ages of RHD were 48.2 and 32.2 years in the control and SCDs groups, respectively (p=0.012). The female ratios of RHD were 88.8% and 46.4% in the control and SCDs groups, respectively. Mitral valve was involved in 58.8%, aortic valve was involved in 32.3%, and tricuspid valve was involved in 8.8% of cases with the SCDs. Interestingly, the tricuspid valve was never involved alone instead together with mitral valve in all of the cases.

Conclusion: SCDs induce severe and chronic inflammatory processes on vascular endothelium all over the body, and terminate with end-organ insufficiencies in early years of life. Beside that SCDs cause a moderate to severe immunosuppression by several mechanisms that may be the cause of higher prevalence of RHD in them.

Key words: Rheumatic heart disease,
sickle cell diseases, chronic endothelial damage,
immunosuppression

## Introduction

Chronic endothelial damage may be the major cause of aging by inducing 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 mainly involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, excess weight, smoking, and alcohol 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 heart disease (CHD), mesenteric ischemia, osteoporosis, and stroke. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are severe and chronic inflammatory processes on vascular endothelium, terminating with end-organ insufficiencies in early years of life. Hemoglobin S (HbS) causes loss of elasticity and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem since sickling is rare in peripheric blood samples of the SCDs 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 various stresses of the body. The hard RBCs induced severe and chronic vascular endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (3, 4). Capillary systems may mainly be involved in the process due to their distribution function for the hard bodies. In another definition, metabolic syndrome is an accelerated atherosclerotic process, and SCDs are an accelerated metabolic syndrome. We tried to understand whether or not there is a higher prevalence of rheumatic heart disease (RHD) in the SCDs.

## Material and Methods

The study was performed in Internal Medicine Units of the Dumlupinar and Mustafa Kemal Universities between August 2005 and April 2016. All patients with the SCDs and cases who had applied for the check up procedure were included. The SCDs were diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused units of RBCs 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 of all study cases 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 fasting plasma glucose, creatinine, hepatic function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, and a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery was performed for all cases. An additional 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 just for the SCDs cases. Other bones were scanned for avascular necrosis according to complaints of the SCDs patients. 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. 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 CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. RHD is diagnosed with the echocardiographic findings, too. Avascular necrosis of bone 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, prevalence of RHD was detected both in the SCDs and control 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 2,855 control cases (1,620 females), totally. Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, $p>0.05$). Mean ages of the control cases were 40.8 versus 41.8 years, respectively ($p<0.001$ for both) (Table 1). Although the significantly higher mean ages and female predominance (56.7% versus 48.5%, $p<0.001$) of the control cases, RHD was detected just in 0.3% of them (eight females and one male). Whereas this ratio was 6.5%

(13 females and 15 males) in the SCDs group (p<0.001) (Table 2). The mean ages of RHD cases were 48.2 ± 16.6 (22-69) and 32.2 ± 8.4 (20-49) years in the control and SCDs groups, respectively (p=0.012). The female ratios of RHD were 88.8% and 46.4% in the control and SCDs groups, respectively. Mitral valve was involved in 58.8%, aortic valve was involved in 32.3%, and tricuspid valve was involved in 8.8% of cases with the SCDs. Interestingly, tricuspid valve was never involved alone instead together with mitral valve in all of the cases. On the other hand, smoking (24.0% versus 6.2%, p<0.001), alcohol (5.0% versus 0.4%, p<0.001), transfused RBCs in their lives (47.6 versus 28.4 units, 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), CHD (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 with the SCDs, significantly. There were 30 mortality cases (16 males) during the ten-year follow-up period (Table 3). 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). Beside that there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR). Although antiHCV was positive in 5.8% (25 cases), HCV RNA was positive just in three cases (0.7%) by PCR.

## Discussion

Chronic endothelial damage may be the leading cause of aging in human beings. It may be the most common type of vasculitis all over the world at the moment. Whole afferent vasculature including capillaries may chiefly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Therefore the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Physical inactivity, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers probably accelerate the process. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases systolic BP further. Although early withdrawal of underlying factors may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, 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 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 severe and chronic endothelial damage, inflammation, edema, and fibrosis terminate with end-organ insufficiencies in early years of life. 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, respectively in the present study. Unfortunately, the great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBCs supports during medical and surgical emergencies in Turkey. Actually, RBCs supports must be given in all medical and surgical emergencies in which there is evidence of clinical deterioration in the SCDs (14, 15). RBCs supports decrease sickle cell concentration in the circulation, and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body. According to our 20-year experiences, simple RBCs transfusions are superior to the exchange. First of all, preparation of one or two units of RBCs suspensions at each time rather than preparation of six units or more provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBCs suspensions at each time decreases the severity of pain, and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBCs suspensions at each time decreases transfusion-related complications in the future. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during transport to the tertiary centers for the exchange. Fifthly, transfusions of RBCs suspensions in the secondary health centers prevent some extra costs on the health system developed during the exchange in the tertiary centers. On the other hand, longer survival 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 stronger physical efforts of male sex in life that may terminate with an exaggerated sickling and an exaggerated chronic endothelial damage in their bodies (17).

RHD is caused by an autoimmune reaction against Group A β-hemolytic streptococci. The majority of morbidity and mortality associated with rheumatic fever is caused by its destructive effects on cardiac valves. It is characterized by repeated inflammation with fibrinous repair. Fibrosis and scarring of valve leaflets, commissures, and cusps leads to abnormalities that can result in valvular stenosis or regurgitation. The valvular endothelium is a prominent site of lymphocyte-induced damage. Normally, T cell activation is triggered by presentation of the bacterial antigens. In RHD, molecular mimicry results in incorrect T cell activation, and these T lymphocytes can go on to activate B cells, which will start to produce self-antigen-specific antibodies. This leads to an immune response attack mounted against tissues in the heart that are misidentified as pathogens. RHD usually occurs after repeated attacks. Rheumatic fever primarily affects children between the ages of 5 and 17 years. In one third of cases, the underlying Streptococcal infection develops without any symptom. On the other hand, some patients develop significant carditis that manifests as congestive heart failure. Unlike typical heart failure, rheumatic heart

**Table 1: Characteristics of the sickle cell patients**

| Variables | Males with SCDs* | *p*-value | Females 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)*** |
| ***Alcohol*** | ***5.0% (11)*** | ***<0.001*** | ***0.4% (1)*** |

*Sickle cell diseases †Nonsignificant (p>0.05)

**Table 2: Comparison of the sickle cell patients and control cases**

| Variables | Patients with SCDs* | *p*-value | Control cases |
|---|---|---|---|
| Number | 428 | | 2855 |
| Female ratio | 48.5% (208) | ***<0.001*** | 56.7% (1620) |
| Mean age of males | 30.6 ± 10.1 (5-58) | ***<0.001*** | 40.8 ± 16.5 (9-85) |
| Mean age of females | 30.1 ± 9.9 (8-59) | ***<0.001*** | 41.8 ± 16.3 (11-88) |
| ***Prevalence of RHD†*** | ***6.5% (28)*** | ***<0.001*** | ***0.3% (9)*** |

*Sickle cell diseases †Rheumatic heart disease

**Table 3: Frequent pathologies of the sickle cell patients**

| Variables | Males with SCDs* | *p*-value | Females with SCDs |
|---|---|---|---|
| Painful crises per year | 5.0 ± 7.1 (0-36) | Ns† | 4.9 ± 8.6 (0-52) |
| ***Transfused units of RBCs‡*** | ***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)*** |
| ***CHD¶*** | ***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) |
| RHD*** | 6.8% (15) | Ns | 6.2% (13) |
| Avascular necrosis of bone | 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 cells §Chronic obstructive pulmonary diseases ¶Coronary heart disease **Chronic renal disease ***Rheumatic heart disease

rheumatic heart failure responds well to corticosteroids, probably due to its autoimmune nature. In Western countries, rheumatic fever has become fairly rare, probably due to the widespread use of antibiotics. Although RHD disproportionately affects women of reproductive age (18), it was detected with a female ratio of 46.4% in the SCDs in the present study. Rheumatic tricuspid valve dysfunction is the rarest of all valvular diseases, and is often associated with left-sided valvular diseases (19). The prevalence of rheumatic tricuspid dysfunction was 8.4% in a previous study (19). In another study, rheumatic tricuspid valve disease was detected with a ratio of 7.7%, and associated mitral valve disease was present in 99.3% of them (20). Similarly, tricuspid valve was involved in 8.8% of cases with the SCDs, and it was never involved alone, instead together with mitral valve in all of the cases in the present study. Mitral valve is involved in 97% of cases with the RHD (21), and mitral stenosis is classically caused by it (22). Whereas mitral and aortic valves were involved in 58.8% and 32.3% of cases, respectively in the present study.

SCDs are severe inflammatory processes terminating with end-organ insufficiencies in early years of life (23). First of all, the SCDs are chronic hemolytic anemias in which the normal lifespan of RBCs decreased from the normal 120 to 15-25 days. Secondly, the severe and chronic endothelial inflammation all over the body causes an overlapping chronic disease anemia in them. Thirdly, the chronic hemolytic process may even cause folate and vitamin B12 deficiencies. Furthermore, end-organ insufficiencies can suppress the immune system of the patients. Frequent acute sinusitis, tonsillitis, and urinary tract infections are the common causes of painful crises and hospitalizations, and they can rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the moderate to severe immunosuppression in such patients (24). For example, tonsillary hypertrophy is a common physical examination finding that may be the result of a prolonged infectious process due to the moderate to severe immunosuppression in them (25). Severe and prolonged endothelial inflammation induced prominent weight loss and cachexia are also frequent findings in the SCDs (4). As a result, menarche is retarded in females with the SCDs (26). Moderate to severe anemias, autosplenectomy, frequent painful crises, hospitalizations, invasive procedures, RBC supports, medications, prevented normal daily activities, and a suppressed mood of the body may just be some of the possible reasons of immunosuppression in the SCDs (27-29). As a result, the significantly higher prevalence of RHD due to repeated bacterial infections should not be an amazing finding in the SCDs.

As a conclusion, SCDs induce a severe and chronic inflammatory process on vascular endothelium all over the body, and terminate with end-organ insufficiencies in early years of life. Beside that SCDs cause a moderate to severe immunosuppression by several mechanisms that may be the cause of higher prevalence of RHD in them.

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