Clinical Research

Evaluation of cardiac function tests in Sudanese adult patients with sickle cell trait

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ABSTRAK

Latar belakang: *Kelainan jantung merupakan komplikasi yang sering terjadi pada anemia sel sabit* (sickle cell). *Bila terjadi bersamaan dengan kelainan paru, maka akan meningkatkan angka kematian. Namun pada* sickle cell trait *(SCT) umumnya tampilan klinis nomal, walaupun ada kelainan genetik. Penelitian ini bertujuan mempelajari hubungan SCT dengan faktor prognostik kardiovaskular dengan mengukur kadar kolesterol HDL, LDL, kreatin kinase jantung (CK-MB), C-reactive protein ultra sensitif (usCRP), homosistein (Hyc), dan* N-terminal pro-brain natriuretic peptide *(NT-pro BNP), pada bangsa Sudan dewasa penyandang* sickle cell trait*.*

Metode: *Suatu studi potong lintang dilakukan pada 200 penyandang SCT dan 200 dewasa sehat sebagai kontrol. Studi ini dilakukan di Khartoum Specialized Hospital, Al-Bayan Hospital, Obayed Clinical Center, dan Dr. Nadir Specialized Hospital, Sudan antara Januari 2015 dan Januari 2016. Seluruh subjek berusia antara 20–32 tahun. LDL -C, HDL-C, CK-MB, NT-pro BNP dan usCRP diukur degan alat analisis kimia otomatis Hitachi 912 (Roche Diagnostic, Jerman), sedangkan homosistein diukur dengan metode ELISA menggunakan kit spesial.*

Hasil: *Kadar LDL-C, hsCRP, dan NT-proBNP lebih tinggi secara bermakna pada kelompok* sickle cell trait *(p<0,001), sedangkan homosistein dan CK-MB lebih tinggi, namun tidak bermakna (p=0,069, dan p=0,054). Sebaliknya, HDL-C pada kelompok SCT lebih rendah dibanding kontrol, namun secara statistik tidak bermakna.*

Kesimpulan: Sickle cell trait *berkaitan dengan meningkatnya faktor risiko kardiovaskuler.*

ABSTRACT

Background: Cardiac dysfunctions have been recognized as a common complication of sickle cell anaemia (SCA), and together with pulmonary disorder accounts for many deaths in these patients. However, sickle cell traits appear clinically normal, although they have genetic abnormality. The aim of this study was to assess the effect of sickle cell trait on cardiac prognostic markers by measuring high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), cardiac creatine kinase (CK-MB), ultra-sensitive C reactive protein (us-CRP), total homocysteine (Hyc), and N-terminal pro-brain natriuretic peptide (NT-pro BNP) tests in adult Sudanese patients with sickle cell trait.

Methods: A cross-sectional study was performed in 200 healthy volunteers as a control group and 200 diagnosed patients with sickle cell trait. It was carried out in Khartoum Specialized Hospital, Al-Bayan Hospital, Obayed Clinical Center and Dr. Nadir Specialized Hospital, Sudan between January 2015 and January 2016. All participants were between 20-32 years old. LDL-C, HDL-C, CK-MB, NT-proBNP and hs-CRP concentrations were measured by Hitachi 912 full-automated Chemistry Analyzer (Roche Diagnostics, Germany) as manufacturer procedure, while homocysteine level was measured by ELISA technique using special kit.

Results: When compared to control group, the levels of LDL-C, hs-CRP and NT-proBNP revealed significant increase in patients' sera (p<0.001), while Hyc and CK-MB levels were increased insignificantly in patients with SCT (p=0.069, p=0.054 respectively). On the other hand, comparison to control group, HDL-C showed insignificant reduction in patients (p=0.099).

Conclusion: The results suggest that sickle cell trait increased the risk of patient-related complication secondary to cardiac dysfunction.

Keywords: cardiac function tests, CK-MB, homocysteine, hs-CRP, NT-proBNP, sickle cell trait

pISSN: 0853-1773 • eISSN: 2252-8083 • http://dx.doi.org/10.13181/mji.v25i3.1412 • Med J Indones. 2016;25:151–5
• Received 24 Mar 2016 • Accepted 31 Aug 2016

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Sicklemia or sickle cell anemia (SCA) includes a group of hematological diseases that are autosomal recessive inherited that includes several genotypes, with a prevalence of hemoglobin S (Hb S).[1] Adults with SCA express both systolic and diastolic cardiac disorder; however the age of violation of dysfunction has not been defined.[2] A few estimates suggest that in excess of 300,000 children are born annually with either SCA or one of its variants or one form of thalassemia.[3] Hb S differs from adult hemoglobin A (Hb A) and is created by substitution of one amino acid in the β-globin gene at 6th position (HBB c.20A>T; p.Glu6-Val).[4] World Health Organization (WHO) estimates that 70% of deaths are avoidable by putting in place "preventive" measures.[5] Between ages 20 and 30 years old, they have renal impairment, pulmonary hypertension, reducing osteonecrosis, retinopathy, leg ulcers, and pain disaster; and at age above 30 years old, they have renal failure and congestive heart failure.[6]

Persons who are heterozygous and have Hb S usually do not show symptoms but the homozygous patients having Hb S (SS) show symptoms of sickle cell disease (SCD) that includes persistent pain, obstructive blood vessel, and inflammation and these symptoms cause high mortality rates in countries with low-income.[7] The sickle cell trait (SCT) is inherited through a sickle cell gene from either parent while the SCD is inherited from two sickle cell genes, one from each of the parent. The symptoms appear in patients with SCD because they have a kind of Hb S that converts normal red blood cells into sickle shapes, the symptoms do not appear in SCT patients because these patients have both normal Hb A and Hb S. The children of SCT patients can inherit the sickle cell gene.[8] Persons with SCT usually do not suffer from symptoms of SCD and live their life normally, but they can inherit the normal gene from one parent (A) and sickle cell (S) gene (AS) to their babies.[9]

Sickle cell trait as well as chronic anemia can lead to heart dysfunction. Young SCA patients have left ventricular hypertrophy, so they need cardiac assessment.[10] Cardiac remodeling is one feature of SCA but for SCT it falls under some suspicions.[11]

This study was envisaged to determine the effects of sickle cell trait on some diagnostic and prognostic biomarkers used for heart problems by measuring high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), cardiac creatine kinase (CK-MB), ultra-sensitive C reactive protein (us-CRP), total homocysteine (Hyc) and N-terminal pro-brain natriuretic peptide (NT-proBNP).

METHODS

This cross-sectional study was carried out in Khartoum Specialized Hospital, Al-Bayan Hospital, Obayed Clinical Center and Dr. Nadir Specialized Hospital, Sudan. The study was carried out between January 2015 and January 2016.

Sample size

The study included 400 participants, 200 were already diagnosed patients with SCT and 200 were normal healthy volunteers as a control group. All participants were between 20–32 years old during the time of collection and all were in normal body mass index (BMI) to avoid confounding influence of weight in the results. Patients on drugs therapy that can affect estimation and/or those with heart and patients who refused to participate were excluded from the study.

Sampling

All the participants signed an informed consent. Data concerning patients and their health information (such as age, tall, weight, health condition, sickle cell disease complications and duration) were obtained using a questionnaire. The ethical committee of Omdurman Islamic University approved the study (No. OIU/resMLS/CCH/53 A).

The patients were asked to fast 8–10 hours before the blood test. Six milliliters of blood through venepuncture was collected from each patient in serum separator tube (SST). The serum separation was done after centrifugation at 3,000 rpm for five minutes. The serum then was assayed for LDL-C, HDL-C, CK-MB, NT-proBNP and high sensitivity C-reactive protein (hs-CRP) by using commercially available kits-Roche/Hitachi cobas systems (Roche Diagnostics,

Germany) as manufacturer procedure. Serum homocysteine was measured using a special kit and ELISA method using AXIS-SHIELD kit (England).[12]

Statistical analysis

The results were compared between sickle cell trait patients with control. The statistical package for social sciences (SPSS) was used. Statistical analysis by student t test with $p<0.05$ considered the significance.

RESULTS

The results of control (n=200) and SCT patient (n=200) groups those were age and BMI matched (p=0.115, 0.204, respectively) were showed in Table 1. The levels of LDL-C (143.21±22.93 mg/dL), hs-CRP (56.61±18.47 mg/L), and NT-proBNP (364.09±38.12 pg/mL) were significantly elevated in SCT patients' sera ($p<0.001$) when compared to control group (108.66±21.70 mg/dL; 35.50±2.15 mg/L, and 219.55±25.37 pg/mL respectively).

The Hyc (6.47±2.08µmol/L) and CK-MB (3.318±1.74 ng/mL) levels were insignificantly modified in SCT patients (p=0.069, 0.054 respectively) when compared to control group (4.92±1.77 µmol/L, 2.944±1.00 ng/mL).

Table1. Comparison of cardiac function tests levels between control and sickle cell trait patients: (mean ± SD)

Groups	Control	Patients	p
Number	200	200	N/A
Age (years)	26.25±5.25	29.50±5.50	0.115
BMI (kg/m2)	22.30±1.05	23.57±3.41	0.204
LDL-C (mg/dL)	108.66±21.70	143.21±22.93	<0.001
HDL-C (mg/dL)	46.67±8.13	43.45±17.16	0.099
us-CRP (mg/L)	35.50±2.15	56.61±18.47	<0.001
Hyc (µmol/L)	4.92±1.77	6.47±2.08	0.069
CKMB (ng/mL)	2.944±1.00	3.318±1.74	0.054
NT-proBNP (pg/mL)	219.55±25.37	364.09±38.12	<0.001

BMI: body mass index; LDL-C: low density lipoprotein; HDL-C: high density lipoprotein; us-CRP: ultra-sensitive C reactive protein; Hyc: total homocysteine; CKMB: cardiac creatine kinase; NT-pro BNP: N-terminal pro brain natriuretic peptide

The HDL-C (43.45±17.16 mg/dL) levels were low in SCT patients when compared to control group (46.67±8.13 mg/dL) but the results were insignificant (p=0.099).

DISCUSSION

Sickle cell trait patients have normal concentration of hemoglobin with normal red blood cells count unlike patients with sickle cell disease. The hemoglobin electrophoresis or high performance liquid chromatography is commonly used diagnosis of SCT. Of the total hemoglobin, around 50-60% is Hb A and sickle 35–45%.[13]

In the present study, there were significant high levels of serum LDL-C ($p<0.001$) in SCT patients (143.21±22.93 mg/dL) compared to controls (108.66±21.70 mg/dL). Otherwise, HDL-C showed insignificant reduction (p=0.099) in patients (43.45±17.16 mg/dL) when compared to control (46.67±8.13 mg/dL). Many studies showed positive associations between SCA (not SCT) and lipid alterations. Rahimi et al[14] reported that the LDL-C and total cholesterol levels in SCD subjects were significantly reduced. Also, Galvão et al[15] affirmed the differences between patients and healthy persons but without specifying the type of lipid and the type of SCA.

Furthermore, in this study, the mean level of us-CRP was increased significantly ($p<0.001$) in serum of SCT patient (56.61±18.47 mg/L) compared to control group (35.50±2.15 mg/L). Our results call attention to indirectly protective role of us-CRP in sickle cell trait leading to increase level in serum. Regardless of age, our results were in line with the report of Krishnan et al[16] whose report included children with chest pain; further, these results were coincided with the results of Okocha et al[17] despite they conducted only Hb SS.

The results of serum NT-proBNP need more concern in this study, whereas the NT-proBNP levels showed highly significant increase ($p<0.001$) in patients with sickle trait (364.09±38.12 pg/mL) when compared to control (219.55±25.37 pg/mL). According to the report of Machado et al,[18] high results of NT-proBNP indicate heart remodeling with the level of BNP or NT-proBNP in the blood

directly related to its severity. Ndumele et al[19] also reported that increased NT-proBNP values are predicting congestive heart failure in adults less than 50 years of age. Accordingly, SCT patient might be suffer from cardiac remodeling although the asymptomatic condition.

Aside from that, Hyc level was found to be insignificantly higher (p=0.069) in patients with sickle cell trait (4.92±1.77 µmol/L) when compared to control group (6.47±2.08 µmol/L). The same pattern in the present study was found in the serum level of CK-MB, that was exhibited as insignificantly elevated (p=0.054) in patients (3.318±1.74 ng/mL) when compared to control (2.944±1.00 ng/mL). The report of Ali et al[20] clarified that elevation of Hyc is not commonly found in sickle cell trait; but if found high that may indicate meningeal vessel thrombosis**.** Nnadi et al[21] stated that creatine kinase test in sickle cell anemia is sensitive for muscular disorder due to sickling particularly in vaso-occlusive crisis more than cardiac disorders.

The significant elevation of serum levels of NT-proBNP, us-CRP, and LDL-C in patient with sickle cell trait synchronously with normal Hyc, CK-MB, and HDL-C documenting that in spite of patients do not suffer from heart dysfunctions, but the sickle cell trait may lead to heart failure in future.

Acknowledgment
Authors are grateful to the V.R Center to provide automated analyzer and its reagents.

Conflict of interest
The author affirms no conflicts of interest in this study.

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