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Original Research Article

Carotid and femoral intima-media thickness in adults with sickle cell disease

Nakul B. Kadam[1], Nikhil O. Bansal[2], Sourya P. Acharya[1]*, Samarth A. Shukla[1]

[1]Department of Medicine, JN Medical College, DMIMSU, Sawangi (Meghe), Wardha, Maharashtra, India
[2]Department of Radiology, Mahatma Gandhi Institute of Medical Sciences and Research Centre, Jaipur, Rajasthan, India

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***Correspondence:**
Dr. Sourya P. Acharya,
E-mail: souryaacharya74@gmail.com

ABSTRACT

Background: This study was conducted to evaluate Carotid Intima Media Thickness (CIMT) and Femoral Intima Media Thickness (FIMT) in adults with SCD.
Methods: The present prospective cross-sectional study with control group was carried out in Department of Medicine at Acharya Vinoba Bhave rural hospital over a period of 6months from January to June 2018. A total of 100 (50 cases of SCD, 50 normal subjects) were studied. In the SCD group, 35 cases were patients regular follow up cases and 15 patients were in sickle cell crisis. CIMT of both left and right carotids were taken and the mean of the two values were recorded. The IMT was also measured in the right common femoral artery (RCFA) and left common femoral artery.
Results: SCD patients in steady state had significantly decreased Hb%, increased WBC counts and platelet counts as compared to healthy controls. The mean right FIMT, left FIMT, right CIMT and left CIMT the patients with SCD with crisis were significantly higher than that of the patients without SCD ($P<0.001$). One way showed that there were significant differences in duration of disease in mean level of Hb%, WBC count, platelet count of the patients in the three groups ($p<0.01$).
Conclusions: CIMT and FIMT can pick up the macrovascular involvement early and can be utilized as screening tools to predict vascular injury so that at risk individuals would be subjected to proper treatment protocols, especially hydroxyurea therapy early on.

Keywords: CIMT, Crisis, FIMT, Hydroxyurea, SCD

INTRODUCTION

Sickle cell disease (SCD) or sickle cell anemia is a lifelong hematologic disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cell's flexibility and results in a risk of various complications. The sickling occurs because of a mutation in the haemoglobin gene. Life expectancy SCD is usually 42 and 48years for males and females respectively.[1] SCD has a high prevalence in India, especially in the central and western regions and poses a considerable health burden.[2,3] As the life expectancy in SCD has increased, other complications have been increasingly recognized. These are retinopathy, vasculopathies, coronary artery disease, pulmonary arterial hypertension, nephropathy etc. Sickle cell anaemia is caused by a point mutation in the β-globin chain of haemoglobin, causing the amino acid glutamic

acid to be replaced with the hydrophobic amino acid valine at the sixth position. Whenever there is hypoxia and stress the β-globin chain promotes the non-covalent polymerization of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these sickle cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia.[4]

SCD also causes an activated adhesive endothelium. These vasculopathy abnormalities are attributable to ischemia-reperfusion injury, hemostatic activation, microvascular occlusion and formation of a procoagulant milieu. Vasculopathy of sickle cell disease has been implicated in the development of pulmonary hypertension, stroke, leg ulceration and priapism, particularly associated with hemolytic severity and reported also in other severe hemolytic disorders. This vasculopathy might also play a role in other chronic organ dysfunction in patients with sickle cell disease.[5-8]

Carotid Intima-Media Thickness (CIMT) is a non-invasive, early marker of atherosclerosis, an increase in this measure may reflect an increase in cardiovascular risk.[9] This is an independent predictor of CVD and may be considered as a surrogate marker for the assessment of subclinical atherosclerosis, inflammation and vasculopathy in SCD individuals.[10] In addition, common femoral arteries have been used for IMT (FIMT) measurements for similar purpose.[11-13] This study evaluated CIMT and FIMT in SCD patients. The aim was to evaluate Carotid Intima Media Thickness (CIMT) and Femoral Intima Media Thickness (FIMT) in adults with SCD. The objectives were to correlate variables like duration of disease, clinical and hematologic profile in SCD patients with and without crisis and to assess CIMT with FIMT in SCD with and without crisis.

METHODS

The present prospective cross-sectional study with control group was carried out in Department of Medicine at Acharya Vinoba Bhave rural hospital which is a 1700 bedded rural tertiary care hospital situated in Wardha District of Central India over a period of 6months from January to June 2018. Due clearance from the IEC was taken before commencement of the study.

A total of 100 (50 cases of SCD, 50 normal subjects) were studied. A total of 50 patients (aged 14-40years) previously diagnosed as SCD by hemoglobin electrophoresis were considered as cases. SCD patients regularly following up at the sickle cell anemia clinic at the hospital (35) and SCD cases who were admitted in crisis (15) were included. Fifty normal subjects were taken as control. The patients with known cardiovascular disease, diabetes, hypertension, collagen vascular disorder, other anemias, chronic kidney disease and patients not giving consent were excluded from the study. Written informed consent was obtained from legal guardians of all study participants.

Thorough history taking and reviewing of patient's medical records were conducted. For SCD patients, history taking included general characteristics, age at diagnosis, history suggestive of the SCD-related complications, number of previous hospitalizations, blood transfusions, episodes of acute chest syndromes and lines of treatment. A complete clinical examination was conducted for all patients including vital signs, anthropometric measurements and systemic examination including cardiovascular, respiratory, abdominal, neurological and ophthalmological evaluation to search for any of the disease complications. Complete blood count and absolute platelet counts were performed for both patients and controls.

Bilateral Carotid Intima-Media Thickness (CIMT) was measured in a 1cm segment of the far wall of the common carotid, 1cm proximal to the flow divider using Aloka prosound in B-mode at AVBRH. Participants were screened in the supine position; the neck was oriented in 45 degree using a custom pillow and B-mode ultrasound images were captured with 7Hz linear array transducer in accordance with the clinical protocol recommended by the American society of echocardiography consensus statement.[14] CIMT of both left and right carotids were taken and the mean of the two values were recorded. Per the latest ESH/ESC hypertension guidelines (2013) carotid IMT >0.9mm has been taken as a marker of asymptomatic organ damage.[15] The IMT was also measured in the Right Common Femoral Artery (RCFA) and Left Common Femoral Artery (LCFA) using the same criteria for IMT and atheromatous plaque definition FIMT.

Statistical Analysis was performed with help of EPI Info (TM) 7.2.2.2 EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC).

Using this software, basic cross-tabulation and associations were performed. Chi-square test was used to test the association of different study variables. t-test was used to compare the means. One-way analysis of variance (ANOVA) followed by Tukeys Critical Difference (CD) was used to compare two means at a time. $p<0.05$ was taken to be statistically significant. Diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated to compare the findings of different diagnostic tools. $P<0.05$ was considered to be statistically significant.

RESULTS

One way Analysis Of Variance (ANOVA) followed by Tukeys Critical Difference (CD) showed that, SCD patients in steady state had significantly decreased Hb%, increased WBC counts and platelet counts as compared to

healthy controls, SCD patients with crisis also had significantly more duration of disease, decreased Hb%, increased WBC counts and increased platelet counts than SCD in steady state patients (p<0.001) (Table 1).

Table 1: Comparison of clinical and hematologic parameters of the three groups.

Parameters	SCD with crisis (n=15)	SCD without crisis (n=35)	Control (n=50)	Test statistic	P value
Age (years)					
Mean±SD	19.80±3.63	21.94±4.68	21.48±3.93		
Median	19	21	21.5	$F_{2,97}$=1.410	0.249 NS
Range	14-28	14-30	14-30		
Gender					
Male: femal	8 (53.3%): 7 (46.7%)	19 (54.3%): 16 (45.7%)	27 (54.0%):23 (46.0%)	χ^2 =0.0038	0.99 NS
Duration of disease (years)					
Mean±SD	10.26±2.15	6.93±2.49	NA		
Median	10	7		t_{48}=8.266	0.006*
Range	2-19	4-12			
Level of hemoglobin (gm%)					
Mean±SD	4.96±1.30	7.20±1.49	13.56±12.84		
Median	5	7.4	12	$F_{2,97}$=7.638	<0.001*
Range	3.0-7.0	4.0-9.5	8.9-102.0		
WBC count					
Mean±SD	16433.33±4911.45	11285.71±2065.56	7176.00±2056.80		
Median	15700	11000	6700	$F_{2,97}$=75.724	<0.0001*
Range	11700-31000	7500 - 17000	4200-11300		
Platelet count					
Mean±SD	4.27±1.18	3.65±0.71	2.03±0.45		
Median	4	3.5	1.95	$F_{2,97}$=89.550	<0.0001*
Range	2.70-6.00	2.80-5.70	0.90-3.00		

*Statistically Significant, NS- Statistically Not Significant

Table 2: Comparison of IMT in both carotid and femoral arteries of the three groups.

Parameters	SCD with crisis (n=15)	SCD without crisis (n=35)	Control (n=50)	Test statistic $F_{2,97}$	P value
Right FIMT					
Mean±SD	0.75±0.14	0.57±0.11	0.55±0.07		
Median	0.7	0.6	0.5	25.393	<0.0001*
Range	0.5-0.9	0.4-0.8	0.4-0.7		
Left FIMT					
Mean±SD	0.69±0.17	0.57±0.10	0.53±0.07		
Median	0.7	0.5	0.5	15.603	<<0.0001*
Range	0.4-0.9	0.4-0.8	0.4-0.7		
Right CIMT					
Mean±SD	0.83±0.15	0.65±0.11	0.66±0.08		
Median	0.8	0.6	0.7	18.557	<0.0001*
Range	0.5-1.0	0.5-0.9	0.5-0.8		
Left CIMT					
Mean±SD	0.85±0.17	0.66±0.11	0.67±0.09		
Median	0.9	0.6	0.7	15.815	<0.0001*
Range	0.5-1.1	0.5-0.9	0.5-0.8		

*Statistically significant, NS- Statistically not significant.

T-test showed that the mean right FIMT, left FIMT, right CIMT and left CIMT the patients with SCD with crisis were significantly higher than that of the patients without crisis and SCD patients in steady state had higher values than normal healthy controls. One-way analysis of variance (ANOVA) followed by Tukeys Critical Difference (CD) showed that there were significant differences in mean right FIMT, left FIMT, right CIMT

and left CIMT of the patients of the three groups (p<0.01) (Table 2).

The diagnostic accuracy, sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of FIMT with respect to CIMT were 88.00%, 50.0%, 100.00%, 100.00% and 86.36% respectively. This suggests that both the tools accurate and more specific to detect subclinical atherosclerosis/vasculitis in SCD patients with crisis. Both CIMT and FIMT can effectively predict abnormal vascular pathologic process in SCD patients who present with recurrent crisis and as the NPV suggests, SCD patients in steady state without crisis have relatively better vasculature (Table 3).

Table 3: Diagnostic accuracy of CIMT/FIMT.

FIMT	CIMT		Total
	With crisis	Without crisis	
With crisis	6 (12.0%)-TP	0 (0.0%)-FP	6 (12.0%)
Without crisis	6 (12.0%)-FN	38 (76.0%)-TN	44 (88.0%)
Total	12 (24.0%)	38 (76.0%)	50 (100.0%)

Diagnostic accuracy of CIMT/FIMT=(TP+TN)/Total cases X 100=88.00%, sensitivity=TP/ (TP+FN) x100=50.0%, specificity=TN/(TN+FP)x100=100.00%, positive predictive value=TP/(TP+FP)x100=100.00%, negative predictive value=TN/(TN+FN) x100=86.36%.

Significant linear positive correlation was found between FIMT and CIMT (r=0.911, p<0.0001). Thus, the value of FIMT significantly increased with CIMT. Both CIMT/FIMT were equally and predictably associated with the vascular pathology. This may indicate any one of these investigations would suffice as an effective tool to assess vascular pathology in SCD (Figure 1).

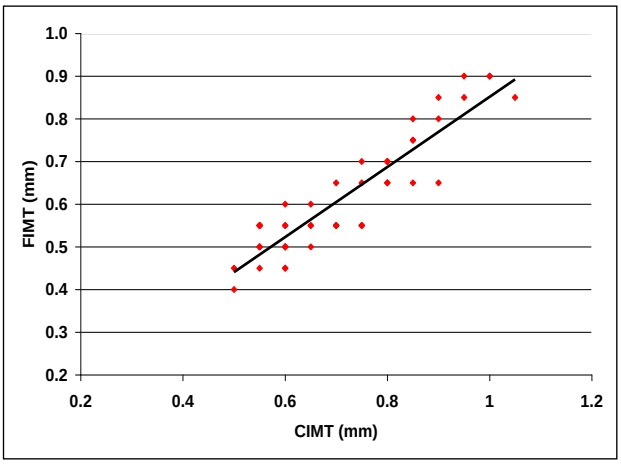

Figure 1: Correlation of CIMT and FIMT in SCD.

DISCUSSION

The mean age of study subjects was 21.94±4.68 in SCD without crisis, 19.80±3.63 with crisis and 21.48±3.93 in control group. There were no significant differences in mean age. In a similar study on SCD by Kaddah NA et al, mean age of cases and control was 10.5 (6.25-14.75) 8 (6-10.75) years respectively.[13] Another similar study by Akibami A et al.[16] The overall mean age of the cases was 23.79±7.81years, and control was 30.43±10.19 years. In present study, no significant differences in male and female ratio was found. Cases and controls were sex matched. A study by Omoti CE et al, were more females 130 (52.8%) than males 116 (47.2%) in this study.[17] As far as duration of disease is concerned, the SCD with crisis group (10.26±4.15) years had significantly longer duration since diagnosis when compared with SCD group without crisis (6.93±2.49)years which was statically significant (p<0.01). Suggesting that longer duration of disease predisposes repeated to crisis.

The mean hemoglobin level of the patients with SCD with crisis (4.96±1.30) was significantly lower than that of the patients without SCD without crisis (7.20±1.49) and control group (13.56±12.84) (p<0.01). In similar study by Kaddah NA et al, hemoglobin of patient with SCD 8.4 (8-8.7) was lower than patient of without SCD 11 (11-12) (P<0.001).[13] Another similar study by Akibami A et al, a mean of haemoglobin concentration and packed cell volume of controls 13.83±1.32g/dl and 43.07±3.95% respectively almost doubles that of cases 7.93±1.47g/dl and 24.44±4.68% respectively.[16] In study by Omoti CE et al, the haemoglobin and hematocrit values in steady state and vaso-occlusive crisis were significantly less than in control (P<0.01).[17]

In another study, Ahemad SG et al, demonstrated that, patients with history of menstruation induced VOC had mean premenstrual values of hematocrit which were not significantly different from the corresponding mean menstrual values of controls.[18] Low hemoglobin levels are associated with unpredictable future clinical outcomes of SCD (Kato GJ et al).[19]

Mean WBC count and platelet count of the patients with SCD with crisis (16433.33±4911.45) were significantly higher than that of SCD in steady state,

(11285.71±2065.56) and controls (7176.00±2056.80) (p<0.01).

In study by Akaddah NA et al, patient with SCD WBC count was significantly elevated than the controls.[13] Another similar study by Akibami A et al, the mean white blood cells count of SCD cases patients were almost double obtained in HbAA controls.[16]

In study by Omoti CE et al, WBC and differential counts in steady state and VOC were significantly higher than in controls (P<0.01).[17] SCD is characterized by abnormally elevated total white cell count, secondary to hyposplenism and inflammation. High white cell count in SCD predisposes to complications like brain infarcts, acute chest syndrome and death. Several other reports revealed a possible association between WBCs and severity of sickle cell disease (SCD).[20-23] Litos M et al, found that SCD patients who developed complications had higher WBC counts than asymptomatic SCD patients.[23] WBC count was found to be an accurate test for detecting acute chest syndrome in SCD patients who attended an emergency department (ED) with pain crises.[24] Castro O et al, noted that WBC count was associated with acute chest syndrome in patients with SCD.[25] Liem RI et al, reported SCD patients with acute chest syndrome had a higher WBC count compared to controls.[26]

In this study, platelet count of the patients with SCD in steady state and with crisis were significantly higher than that of control (p<0.01). Ahemad SG et al, studied the platelet levels in menstruation induced vaso-occlusive crisis (VOC) in SCD females.[18] The mean menstrual platelet count in SCD females was significantly higher than the mean premenstrual value suggesting that increased platelet counts may have been associated with VOC.

Another similar study by Akibami A et al, mean platelet counts for the cases were 412.71±145.09*103/µl and for the controls 222.82±57.62*103/µl which is almost 100% higher in cases compared to control. Omoti CE et al, study also concluded the same.[14,16]

Freedman ML et al, followed asymptomatic adults with SCD with high platelet counts 1.7-fold (mean, 438, 398 +/-86,223) and mega thrombocyte numbers, 2.3-fold (mean, 79,535 +/-38,907) for 6months.[27] Over this, 6months' time all patients had elevated platelet counts. The study concluded that the explanation of this high platelet counts and mega thrombocytes was because of lack of splenic sequestration.

Villagra J et al, in their study concluded that, increased platelet activation is common in SCD and pathologic platelet activation is a risk factor for development of thrombosis and pulmonary hypertension in SCD.[28]

In this study, the mean episode of crisis (mean±SD) of the patients with SCD with crisis was 3.20±0.77 with range 2-4 and the median was 3. In Akaddah NA et al, number of vaso-occlusive crises/year was 4 (2-8), which was comparable.[13] In this study, mean of right CIMT, left CIMT, right FIMT and left FIMT the patients with SCD with crisis were significantly higher than that of the patients without SCD (p<0.01). One way showed that there were significant differences in mean right CIMT, left CIMT, right FIMT and left FIMT of the patients of the three groups (p<0.01).

In study by Akaddah NA et al, CIMT values in patients (median 0.42, range 0.32-0.6mm) were significantly higher compared to controls (0.36, 0.34-0.45 mm), P=0.03.[13] Both right and left CIMT values for SCD patients were also significantly higher than in corresponding values for controls: P=0.014 and P=0.008, respectively. Tantawy AA et al, in their study also demonstrated that CIMT was significantly higher in patients with SCD compared to controls (P <0.001).[29]

Kaddah NA et al, studied CIMT values in SCD.[13] The study showed that CIMT values were significantly higher in SCD patients (median 0.42, range 0.32-0.6mm) compared to controls (0.36, 0.34-0.45mm), P=0.03. CIMT correlated positively with age (r=0.460, P=0.011) and total number of vascular incidents necessitating hospital admission (r=0.439, P=0.015). This suggests that inflammation and vasculopathy resembling atherosclerosis is an ongoing process in SCD.

Belizna C et al, studied carotid arterial stiffness, intima-media thickness and transcranial doppler ultrasonography in adults with SCD. The study concluded that arterial stiffness is a predisposing factor for development of stroke in SCD.[30]

Abo-Zenah H et al, studied the spectrum of kidney functional and structural alterations in sickle cell hemoglobinopathy (SCH). In this study, CIMT and proteinuria were evaluated as surrogate markers of cardiorenal disease in SCD. Preclinical atherosclerosis (increased CCA IMT and/or atheromatous plaques) was noticed in 68.8% of SCH individuals with increased UAE (ANOVA p=0.003). The study concluded that markers of cardiorenal risk such as albuminuria and IMT are common findings in SCH patients and could be useful screening tools to identify sicklers at risk for cardiovascular and renal events.[31]

When author compared CIMT to FIMT in this study, both of these parameters were comparable in detection of vasculopathy. The diagnostic accuracy of CIMT/FIMT was 88%, specificity was 100%, positive predictive value was 100% and negative predictive value was as high as 86.36%. CIMT and/or FIMT can be used as screening tool to predict vasculopathy in SCD.

CONCLUSION

SCD patients have signs of inflammation and vascular insult early in life and may be at risk of developing premature atherogenic changes. Longer duration of disease, increased number of crisis, decreased hemoglobin, increased WBC and platelet counts all contribute to the inflammatory and vasculopathy changes. Endothelial dysfunction super added by hypoxia and free radical damage adds to the microvascular damage. Inability of the microvasculature to respond to vasodilators like nitrous oxide, along with inflammation contributes to atherosclerosis like injury.

CIMT and FIMT can pick up the macrovascular involvement early and can be utilized as screening tools to predict vascular injury so that at-risk individuals would be subjected to proper treatment protocols, especially hydroxyurea therapy early on.

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