

Sickle cell disease prevents diabetes mellitus occurrence: A hospital based cross-sectional study

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ABSTRACT

Background: Sickle cell disease is the commonest inherited hemoglobinopathy. There are few reports point towards decrease incidence of diabetes mellitus in sickle cell disease patients. **Materials and Methods:** This cross-sectional study was conducted in VIMSAR, Burla, Odisha between Nov 2014 to Oct 2016. FBS and 2 hours OGTT reports of adult sickle cell disease patients were compared with the same reports from equal no of adult persons without sickle cell disease (controls) to found out any significant difference in prevalence of diabetes mellitus in sickle cell disease patients versus controls. **Results:** A total of 137 adult patients of sickle cell disease out of which males were 94 (68.61%) and females were 43 (31.38%) with an average age of (26.7 ± 10.9) years and an equal number of controls [males 87 (63.8%) and females 50 (36.5%)] with an average age of (47.6 ± 13.6) years were included in the study. We found diabetes mellitus in 2 (1.46%) out of 137 sickle cell disease patients with an average BMI 18.5 kg/m² versus 12 (8.76%) in equal number of controls with an average BMI of 22.6 kg/m². **Conclusion:** This study concludes that prevalence of diabetes mellitus in sickle cell disease patients is significantly lower than non-sickle cell disease persons. This may be due to less longevity and low BMI in sickle cell disease patients.

Keywords: Diabetes mellitus, prevalence, sickle cell disease

Introduction

Sickle cell disease (SCD) is caused by mutation in β -globin gene and is the commonest inherited hemoglobinopathy.^[1] Infections, chronic renal failure, and chronic cardiopulmonary complications are common causes of death among sickle cell disease patients and so also in diabetes mellitus (DM) patients.^[2,3]

Although there are no strong population-based data to determine the relatively less prevalence of diabetes mellitus among patients with sickle cell disease, it seems sickle cell disease population enjoys a relative protection from diabetes mellitus. There are no satisfactory explanations for the uncommon association

of these two diseases. One explanation is that majority of patients with sickle cell disease die early, therefore, relatively small number of patients survive for the clinical manifestation of diabetes mellitus.^[4] However, sickle cell disease found in India (Asian haplotype) is less severe than African haplotype and a significant proportion of patients survive more than 30 years of age.^[5] Despite longer survival, there are no studies which focus co-existence of diabetes mellitus and sickle cell disease from India.^[5,6] Other theoretical mechanism for such protection would indicate the low Body Mass Index (BMI) and hyper metabolism, which cause decrease incidence of diabetes mellitus in SCD patients. Also there may be a genetic mechanism by which sickle cell disease may inhibit the development of diabetes mellitus.^[7]

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Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_466_18

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How to cite this article: Prusty B, Soren T, Choudhury A, Biswal R, Pradhan DK, Thatoi PK. Sickle cell disease prevents diabetes mellitus occurrence: A hospital based cross-sectional study. J Family Med Prim Care 2019;8:361-4.

It is well known that India harbors world's second largest diabetic population i.e. 8.8% of adult population^[8] and Odisha, one of the eastern states of India has high prevalence of SCD patients with prevalence ranging from 5 to 30% particularly western part of Odisha.^[9,10]

Veer Surendra Sai Institute of Medical Science and Research (VIMSAR), Burla is situated in western Odisha, catering a population of 8–10 millions. A large number of patients with sickle cell hemoglobinopathy attend the sickle cell clinic and medicine OPD and get admission into medicine ward. The aim of this study is to assess whether patients with SCD have the same prevalence of diabetes mellitus as the general population of other parts of Odisha.

Materials and Methods

After obtaining permission from Institutional Ethics Committee (IEC), a cross-sectional study was designed in the Department of General Medicine, Sickle Cell Clinic and Molecular Biology Laboratory of VIMSAR, Burla, Odisha from November 2014 to October 2016.

Patient selection

Diagnosed and suspected SCD patients admitted to medicine indoor were considered for the study according to the following criteria.

Inclusion criteria: Persons more than 15 years of age with either,

1. Previously diagnosed as Sickle Cell Disease
2. Newly detected as Sickle Cell Disease
3. Patients of Sickle Cell Disease with Diabetes Mellitus.

Exclusion criteria: Persons with either,

1. Family history of Diabetes Mellitus
2. Below 15 years of age
3. Persons not giving consent.

Controls: An equal number of persons were taken as controls for study who were,

1. Negative for sickle cell hemoglobinopathy admitted to medicine indoor for other reasons
2. Given consent for study.

Sample: Sample size for the study was calculated to be 111 considering the prevalence of SCD in Odisha to be 7.5% with an absolute precision of 5%. Taking a non-response rate of 10%, the estimated sample size was 123. A total of 274 participants were included in the study which consists of 137 participants each in SCD cases and control group.

Each individual participated in the study was subjected to careful history including family history of diabetes mellitus and a thorough clinical examination. BMI was calculated for every individual. Table 1 shows patients presented with various clinical symptoms and signs of SCD.

Table 1: Clinical feature of SCD patients (n=137)

Clinical feature	Number of cases (%)		
	Male	Female	Total
VOC	50 (68.5)	23 (31.5)	73 (53.28)
Fever	22 (64.7)	12 (35.3)	34 (24.81)
Anemia	7 (53.8)	6 (46.2)	13 (09.49)
jaundice	7 (100)	0 (0)	7 (5.11)
AVN	4 (66.7)	2 (33.3)	6 (4.38)
Osteomyelitis	3 (100)	0 (0)	3 (2.19)
Dactylitis	1 (100)	0 (0)	1 (0.73)

Investigations

All cases and controls were tested for fasting blood sugar, 2 hr OGTT, sickling test, hemoglobin electrophoresis (hemoglobin S and fetal hemoglobin percentages), and other routine tests. Patients were categorized according to WHO diagnostic criteria for diabetes mellitus e.g. diabetes mellitus, impaired fasting glucose or impaired glucose tolerance and no diabetes mellitus (normal blood sugar levels). We have not tested hemoglobin A1c to diagnose or rule out DM as this measurement is unreliable in the setting of sickle cell disease.^[11,12] The persons participated in the study were recognized as having no diabetes mellitus after having two normal levels of fasting blood sugar or 2 hr PPBS or random blood sugar on two separate days. Sickle cell disease was confirmed by sickling test followed by hemoglobin electrophoresis by Bi-directionally interfaced fully automated HPLC system by BIO-RAD.

Data analysis

Data was entered using Microsoft Excel 2010 and analyzed using Statistical Package for Social Sciences version 18 (PASW statistics for Windows, Chicago: SPSS Inc.).

Descriptive statistics were used and the results were expressed as mean \pm standard deviation or frequency and percentage. Normally distributed quantitative and categorical variables were compared using Students *t*-test and Pearson Chi-square test respectively. Odds ratio with 95% confidence interval was calculated and an asymptotic 2-tailed *P* value of <0.05 was considered significant.

Results

A total of 137 cases of sickle cell disease were included in the study with various symptoms [Table 1], out of which 94 were males (68.61%) and 43 were females (31.38%). The mean age of patients with SCD was 26.7 (± 10.4) years. An equal number of controls were included out of which males were 87 (63.5%) and females were 50 (36.5%) with an average age of 47.6 (± 13.6) years [Table 2]. The mean BMI among the SCD patients and controls were 18.5 kg/m² vs 22.6 kg/m² [Table 2].

The most common clinical presentation for hospital admission among patients with SCD was VOC (vaso-occlusive crisis),

followed by fever, anemia, jaundice, AVN (avascular necrosis), osteomyelitis, and dactylitis [Table 1].

As per WHO criteria for diagnosing diabetes mellitus (DM present: FBG ≥ 126 or OGTT ≥ 200 ; DM absent: FBG < 126 and OGTT < 140), only 1.46% of SCD patients ($n = 2$) had overt diabetes mellitus. From the above 2 cases of SCD with diabetes mellitus, one person aged 21 years had Type-1 DM and the other person aged 46 years had Type-2 DM. Among the control group, 8.76% had diabetes mellitus ($n = 12$). The difference of diabetic cases among the SCD group and control group was statistically significant (P -value = 0.006) with odds ratio of 0.154 (95% CI: 0.034-0.703) [Table 3].

Bar diagram in Figure 1 shows the distribution of diabetic cases among SCD patients and Control group [$n = 2$ (1.46%) Vs $n = 12$ (8.76%)].

Discussion

The homozygous point mutation in the beta-globin chain of hemoglobin at 6th position (Glu6Val mutation) results in sickle cell disease, while the heterozygous mutation results in sickle cell trait.^[12] Patients with sickle cell disease require comprehensive care including preventive interventions, pain management, hydroxyurea, and blood transfusion.^[13] Managing patients with SCD is challenging as patients present with various symptoms, most common being the vaso-occlusive crises followed by fever and anemia. Few patients progress to adulthood owing to early mortality from the complications of sickle cell disease as well as from complications of recurrent blood transfusion like iron overload, cirrhosis, and heart failure.^[2,13] In the present study, majority of the patients were below the age of 20 years (40%) followed by patients in the age group 21–30 years (34%). Rest 26% of the patients present after the age of 30 years most likely due to increase in HbF (fetal hemoglobin) level (protective factor), and increase awareness of the disease resulting in decreased mortality. Due to the complex and disabling nature

of SCD, appropriate ambulatory management is critical to avoid acute pain, vaso-occlusive episodes, and hospitalizations.^[13]

Past studies have reported a low prevalence of diabetes among the sickle cell disease patients.^[14,15] Outcomes of the study conducted by Al Harbi *et al.* suggested sickle cell disease and sickle cell trait patients are protected from development of diabetes as well its complications.^[14] The protective nature of sickle cell disease against diabetes may be due to abnormal hemoglobin which act as a buffer and absorbs large amounts of glucose.^[14] The cause of infrequent occurrence of diabetes mellitus in SCD patients can also be due to low BMI and lower life span.^[16,17] In our study, the average age and body mass index in SCD patients and controls were 27 years, 18.5 kg/m² and 32 years, 22.6 kg/m², respectively. The ages of both the groups are comparable with low body mass index in SCD patients. Zhang *et al.* reported age and BMI were two strong environmental factors determining the prevalence of diabetes in SCD patients.^[15] In this study only 2 (1.46%) persons among sickle cell disease group are diabetic whereas 12 (8.7%) persons are diabetic from controls. This result suggests sickle cell disease patients have some protection towards development of diabetes mellitus. Researchers claim if the protective effect of sickle cell trait is verified, potential novel glucose buffering agents can be used as pharmacotherapy for diabetes mellitus.^[14] Morison (1979) in a study of 186 sickle cell disease patients could not find a single case of diabetes mellitus.^[16] Ali A. Mohamed *et al.* in a cross sectional study among SCD patients in Bahrain population between 2003 to 2010 found that the prevalence of diabetes mellitus in SCD patient is lower than Bahrain population, indicating SCD may have protective effect towards diabetes mellitus development.^[17]

Patients with chronic diseases like SCD and diabetes mellitus require regular monitoring by healthcare team in order to provide quality care. Family physicians and primary care doctors have an important role in providing guidance to the SCD patients and their family members on various aspects of the disease.^[18] Since SCD is diagnosed at an early age of life and the treatment is scheduled at regular intervals, a healthy patient-physician

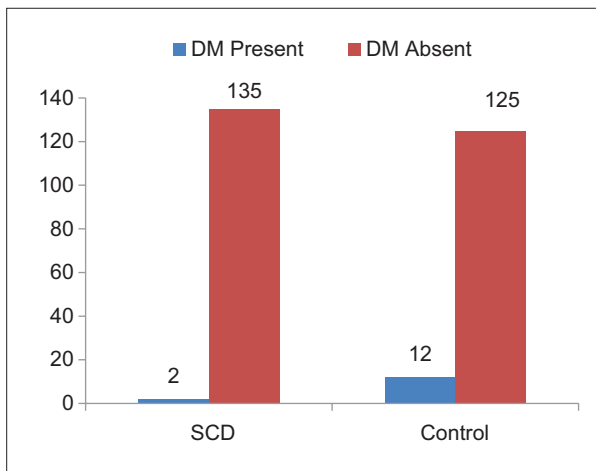


Figure 1: Bar diagram showing no. of diabetic cases among SCD and control group

Table 2: Demographic and clinical parameters of cases and controls (n=274)

Parameters	SCD (n=137)	Control (n=137)	P
Age (years)	26.7±10.4	47.67±13.6	<0.001
Sex			
Male	94 (68.61)	87 (63.5)	
Female	43 (31.38)	50 (36.5)	0.372
BMI (kg/m ²)	18.5±2.3	22.6±3.4	<0.001

Table 3: Diabetes mellitus status in SCD (n=137) and controls (n=137)

Diabetes Mellitus	SCD patients (n=137)	Controls (n=137)	OR (95% CI)	P
DM Present n (%)	2 (1.46%)	12 (8.76%)	0.154	0.006
DM Absent n (%)	135 (98.54)	125 (91.24)	(0.034-0.703)	

relationship is mandatory for follow-ups. Though both SCD and diabetes patients can be managed by family physicians, studies report that patient always directly seeks help from blood center and hematology specialists.^[18] Xavier *et al.* reported that the closeness or contact between persons with SCD and primary care physicians is almost non-existent.^[18] The weak bonds are of concern as strengthening the bonds between family physicians and SCD patients is critical in reducing morbidity and mortality.^[13,18] SCD patients with diabetes need not always require to be seen by hematologist or endocrinologist at every moment as their hectic appointments will lead to loss of follow-ups. On the contrary the closer associations between SCD patients and family physicians will allow the monitoring of these patients smoothly through their lives.^[18]

Our study was new in this category as the prevalence of both DM and SCD is significantly high in our population. Although our sample size is low, it is adequate and certainly it throws some light towards non-coexistence of diabetes mellitus and SCD. The study was conducted in a tertiary care hospital in admitted SCD patients, not representing the socioeconomic and demographic pattern of the community. The controls were non-SCD patients admitted to medicine ward for other health-related issues were not absolutely healthy.

Conclusion

The occurrence of diabetes mellitus in SCD patients is low in comparison to control population. This may be explained by lower life span, hyper metabolic state, and low body mass index in SCD patients. Alternatively, there may be a genetic or epigenetic protective effect of SCD towards development of diabetes mellitus. Further, additional research is recommended to identify the potential protective factors of SCD towards development of diabetes mellitus and large-scale study is required in the community level to prove sickle cell disease protects against diabetes mellitus.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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