

Original Research Article

Study of diabetes mellitus among patients with sickle cell disease

Prafulla Kumar Bariha*, Biswaranjan Prusty, Manoj Kumar Mohapatra

Department of General Medicine, VIMSAR, Burla, Odisha, India

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***Correspondence:**

Dr. Prafulla Kumar Bariha,

E-mail: drpkbariha@gmail.com

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) occurs when impaired insulin effectiveness is accompanied by decreased insulin production by β cells. With 366 million people diagnosed in 2011 and a trend of increasing prevalence worldwide (Lyssenko and Laakso 2013), diabetes is one of the major threats to human health. Objectives of the study were to assess the occurrence of diabetes mellitus in sickle cell disease (SCD) patients and to study glycemic status of patients with SCD and clinical presentation.

Methods: An observational study was done at department of general medicine and sickle cell clinic and molecular biology laboratory, Veer Surendra Sai institute of medical science and research, Burla between November 2014 to October 2016. All recorded data analyzed through standard statistical methods including standard diagram and groups and finding were discussed in detail to draw appropriate conclusion, through standard statistical methods including standard diagrams.

Results: The study was taken on 137 cases of SCD patients admitted at VIMSAR, Burla. Sex distribution of SCD patient with male (68.81%) and female (31.38%) clinical feature of SCD patients shows VOC (vaso occlusive crisis) was the most common presentation for hospital admission followed by fever, anemia, jaundice, AVN (avascular necrosis), osteomyelitis, dactylitis. The most of SCD are having normoglycemic with most of diabetes mellitus are in control group. Glycemic status in SCD cases and controls with 6.57% cases of SCD, 13.14% of controls are hyperglycemic.

Conclusions: The majority of patients in this SCD patients were between the age group 15-20 years. The occurrence of diabetes mellitus in SCD patients is low in compare to control population. Showing impairment of glucose tolerance in SCD but low presence of diabetes mellitus. presence of lower life span of RBC, hypermetabolic state and low body mass index in SCD patients.

Keywords: SCD, VOC, AVN, HPLC, T2DM

INTRODUCTION

Sickle cell hemoglobinopathy is caused by mutation in β globin gene result in formation of sickle hemoglobin. This inherited haemoglobinopathy in the homozygous state is called SCD and in heterozygous state is called sickle cell trait. Sickle cell hemoglobinopathy has protean manifestation. The term SCD refers to homozygous or compound heterozygous states of hemoglobin.

High baseline metabolism and low body mass index (BMI) by Barden et al may provide protection from T2DM in SCD by Morrison et al.^{1,2} Past studies suggested a low prevalence of diabetes in patients with SCD.¹

Clinical experience in tropical countries with a high incidence of SCD indicates that the concurrence of sickle cell disease with either type-I or type-2 diabetes is a rare finding.²

Although there are no population-based data to determine the relative prevalence of diabetes among patients with sickle cell disease in tropics, it seems that the sickle cell disease population enjoys relative 'protection' from diabetes. Theoretical mechanism for such protection would indicate the low BMI, hypermetabolism and possibly other genetic factors. There are no satisfactory explanations for the uncommon association of these two diseases. One explanation is that majority of patients with sickle cell anemia died early, therefore, relatively small number of patients survived for the clinical manifestation of diabetes.³ However, sickle cell anemias found in India and Saudi Arabia (Asian haplotype) is less severe than African haplotype and a significant proportion of patients survived more than 30 years of age.⁴ In spite of longer survival, concurrent diabetes with sickle cell anemia has not been reported from India.^{4,5} Hence, some other unknown factor(s) may be responsible for this rare association. Another explanation is genetic. In support of this hypothesis is the fact that both the β -globin and the insulin genes are present in short arm of chromosome 11. It is not known whether the genetic loci of insulin and β -globin have any inhibitory effect on the inheritance pattern or penetrance of the other. Therefore, the relation between diabetes mellitus and sickle cell anemia needs further evaluation.

VIMSAR, Burla is situated in Western Odisha, catering a population of 8-10 million, large numbers of patients of sickle cell haemoglobinopathy attend medicine OPD and admitted in Medicine ward. Sickle cell disease is highly prevalent in western Odisha ranging from 5 to 30%.⁶ No detail study has been done regarding diabetes mellitus in patients with sickle cell diseases. Keeping all these facts in mind the study was undertaken.

METHODS

The study was conducted in sickle cell disease patients admitted to Veer Surendra Sai institute of medical sciences and research, Burla during November 2014 to October 2016.

SCD on the patients admitted to medicine indoor. Suspected sickle cell disease patients found positive after subjected to sickling test, β electrophoresis, high performance liquid chromatography (HPLC).

Inclusion criteria

Patient previously diagnosed as SCD ≥ 15 years, admitted to medicine indoor. New patient diagnosed as SCD. Patient of SCD with diabetes mellitus.

Exclusion criteria

Excluded patients with family history of diabetes mellitus, patients age below <15 is excluded and patient not giving consent. An equal number of controls were taken for study who are having negative for sickle cell

hemoglobinopathy admitted to medicine indoor and giving consent for study.

Tests

Sickling test, hemoglobin electrophoreses, HPLC, glycosylated hemoglobin, fasting plasma glucose and oral glucose tolerance test, oral glucose tolerance test, interpretation and other investigations: hemoglobin estimation (Hb%). This was done by Sahli's acid hematin method, differential count and comment on peripheral smear, blood smear was drawn and stained with Leishman's stain (Wintrobe, 1967), differential count was done and red cell morphology was studied, total leukocyte count by using Turk's solution and Thomas dilution pipette in the conventional method, ESR-by Westergren method, Serum creatinine-by alkaline picrate method, urine examination, urine albumin by boiling test, 24 hour urinary protein was measured whenever required, presence of hematuria by Benzidine test, presence of sugar by Benedicts test, microscopic examination was done and sent for culture whenever required, plain X-ray abdomen-to look for pancreatic calculi, USG of abdomen-to assessment of pancreatic status, pancreatic calculi, CT Scan of abdomen- to access for pancreatitis and pancreatic calculi.

RESULTS

In the present study total of 137 cases of SCD were taken for evaluation. SCD was confirmed by sickling test followed by hemoglobin electrophoresis and HPLC method. The SCD patients were tested for diabetes mellitus criteria and routine investigations. Age and sex wise distribution of cases in the range (15-20 years) is 39.42% and (21-30 years) is 33.58%. Age and sex wise distribution of controls of which majority in the range (15-20 years) is 29.93% and (21-30 years) is 27.74%. Clinical feature of patients shows VOC (vaso occlusive crisis) was the most common presentation for hospital admission.

Table 1 shows most of SCD are having normoglycemic with most of diabetes mellitus are in control group, with a p value <0.05 .

Table 1: Clinical feature of SCD patients.

Clinical feature	Number of cases	Percentage (%)
VOC	73	53.28
Fever	34	24.81
Anemia	13	09.49
Jaundice	7	05.11
AVN	6	04.38
Osteomyelitis	3	02.19
Dactylitis	1	00.73

This Table 2 shows diabetes mellitus in SCD patients and controls with 2 (1.46%) in SCD are DM and 12 (8.76%) are in control are having DM, p value <0.05.

Table 2: FBG status in SCD patients and controls.

FBG (mg%)		<100	100-125	≥126	Total
SCD patients	No.	128	07	02	137
	%	93.43	05.11	01.46	100
Controls	No.	119	06	12	137
	%	86.86	4.38	8.76	100

Chi square=7.548, Degree of freedom=2, p value=0.023

Table 3 shows diabetes mellitus in SCD patients and controls with 2 (1.46%) in SCD are DM and 12 (8.76%) are in control are having DM, p value <0.05.

Table 4: Hyperglycemia and normoglycemia in SCD patients and controls.

Glycemic status		Hyperglycemia (FPG ≥100 mg%)	Normal glucose tolerance (FPG <100 mg%)	Total
SCD patients	No.	09	128	137
	%	06.57	93.43	100
Controls	No.	18	119	137
	%	13.14	86.86	100

Chi square=3.328, degree of freedom=1, p value=0.068

DISCUSSION

SCD refers to homozygous or compound heterozygous states of hemoglobin's, which involved two abnormal allelomorph genes related to hemoglobin formation, at least one of which is sickle cell gene. The genotype constitutes SCD are SS, SC, S-Thal, SE, SF, SD etc. In Western Odisha the gene frequency among the general population is 15.1% as reported by Kar et al.

Recent data shows sickle cell hemoglobinopathy is highly prevalent in western Odisha ranging from 5 to 30%.⁶

The gene is not confined to only tribal people but throughout the society being more frequent in scheduled caste and some other caste in Hindus. In the present study 137 cases of sickle cell disease were taken with equal no of controls. Of the 137 cases of sickle cell disease patients 94 (68.61%) are male and 43 (31.38) are female, with a comparatively higher no of male study being carried out in a tertiary care level. The majority of patients were younger as 54 cases (39.48%) are in 15-20 years range, 46 cases (33.58) were in 21-30 years range. Other cases were distributed as 20 (14.6%) in 31-40 year, 12 (8.76%) in 41-50 years and above 50 years are 5 (3.65%). The higher age group of presentation of SCD is most likely due to increase HbF (fetal hemoglobin) level (protective factor), and increase awareness of the disease resulting in decreased mortality.

Table 3: Diabetes mellitus status in SCD and controls.

Variables		DM Present	DM Absent	Total
SCD patients	No.	2	135	137
	%	01.46	98.54	100
Controls	No.	12	125	137
	%	08.76	91.24	100

Chi square=7.52, degree of freedom=1, p value=0.006

This Table 4 shows glycemic status in SCD cases and controls with 9 (6.57%) cases of SCD, 18 (13.14%) of controls are hyperglycemic.

The average age and body mass index in SCD patient are 27 years and 18.5 kg/m² respectively. In controls the average age is 32 years and BMI are 22.6 kg/m². The age of both groups is comparable with low body mass index in SCD patients.

The cases were presented as 73 (53.28%) vaso occlusive crisis, 34 (24.81%) fever, 13 (9.49%) anemia, 7 (5.11%) jaundice and low presence of a vascular necrosis, osteomyelitis, dactylitis as 4.38, 2.19 and 0.73% respectively. Painful crisis is more common in sickle cell disease and mostly in young age.

In this study glycemic status among sickle disease and controls cases by doing FPG and 2-h PG. After comparing the FPG values in SCD patients and controls, in SCD patients out of 137, normal FPG <100 mg% were 128 (94.43%) in compare to FBG <100 mg% in control was 119 (86.86%). The impaired fasting glucose in SCD were 07 (5.11%) as compared to 12 (8.76%) in controls. The diabetes was 02 (1.46%), 12 (8.76%) in SCD and control respectively. This shows most of SCD are having normoglycemic with most of Diabetes mellitus are in control group, with a p value <0.05.

The occurrence of diabetes in SCD patient was very low, 2 (1.46%). Mean age of presentation of SCD patient were 26.73 years. One SCD patient was 21 years age and the other one was 54 years age. The 21-year diabetes patient was having diagnosed as type 1 DM having sickle cell disease and the other patient was 56-year age. Compare

to SCD cases the control was having 12 (8.76%) as diabetes mellitus and 125 (91.24%) as non-diabetic, which shows occurrence of diabetes is low in SCD with a significant p value <0.05.

Morison et al in a study of 186 sickle cell disease patients could not find a single case of diabetes mellitus. The higher age group of SCD patients with diabetes mellitus could be due to effect of glycosylation of sickle hemoglobin nullifying some pathological effect of sickle hemoglobin hypothesis made by Reid.⁷

The cause of infrequent occurrence of diabetes mellitus in SCD patients is probably due to rarity of obesity and the relatively small numbers of patients entering the age group of maturity onset diabetes Serjeant.⁸

Mohamed et al in cross sectional study in 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.⁹

Further comparing glycemic status of SCD with control as normoglycemic (FPG <100 mg%) and hyperglycemic (FPG ≥100 mg%), it showed in SCD patients 9 (6.57%) are hyperglycemic in compare to 128 (93.43%) as normoglycemic. Controls having 18 (13.14%) as hyperglycemic and 119 (86.86%) are normoglycemic, with p value of 0.068. Indicating that occurrence of impaired glucose tolerance is high in SCD patients in compare to non-SCD patients. Peculiarly the occurrence of diabetes mellitus in SCD patient is low in compare to normal population.

The mean HbA_{1c} in SCD patients and controls were 4.3 and 5.1% respectively. The lower value of HbA_{1c} in SCD patients may be due to short survival of red blood cells. Schnedl et al reported that several hemoglobinopathies cause false HbA_{1c} results. SCD causes the lifespan of the red blood cell to be shortened to approximately 10-14 days (the normal lifespan is ~120 days). The HbA_{1c} measurement in a person with SCD would, therefore, not accurately reflect glycemic control over a 3-month period as normally expected because the red blood cells do not have time to become glycosylated before being removed from circulation.^{10,11} Consequently, the measured HbA_{1c} might be spuriously low.

Although diabetes is low in SCD patients with significant number of prediabetes in SCD patient in this study. Further study is required in sickle cell trait and in community level in large scale basis. 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 patient were admitted to medicine indoor for other health related issues are not absolute healthy.

CONCLUSION

During the study period 2014 to 2016, 137 SCD cases of SCD patients were examined of 68.61% of patients were males as compared to 31.38% of females. The majority of patients in this SCD patients were between the age group 15-20 years was 39.42% and between 21-30 years was 33.58%. VOC (vaso occlusive crisis) (53.28%) was the most common clinical feature in the patient followed fever (24.81%) and anemia (9.49%), jaundice, osteomyelitis, dactylitis in the decreasing order. The occurrence of diabetes mellitus in SCD patients is low in compare to control population. Comparing the FPG in SCD and controls as normoglycemic (FPG<100 mg%) and hyperglycemic (FPG >100 mg%) there is significant increase in hyperglycemia in SCD patients. Thus, showing impairment of glucose tolerance in SCD but low presence of diabetes mellitus. This may be explained by the presence of lower life span, hypermetabolic state and low body mass index in SCD patients.

Alternatively, there may be a genetic or epigenetic protective effect of SCD towards development of DM. Further, additional research is recommended to identify the potential protective factors of SCD which may have a protective effect against the development of diabetes mellitus at community level.

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