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INTRODUCTION

Thalassemias are a group of hereditary diseases caused by genetic mutations in hemoglobin genes which result in reduced or null production of one or more globin chains and is the commonest innate haemoglobinopathy that affects significant people across the globe. It is inherited as an autosomal recessive disorder.¹ Beta thalassemia is more common, based on clinical severity and hereditary pattern. It is classified into transfusion-dependent thalassemia, non-transfusion-dependent thalassemia, and carriers.² In Pakistan, the frequency of thalassemia patients is 5 to 8% resulting in annually more than 5,000 births of transfusion-dependent thalassemia patients.³ Patients with transfusion-dependent thalassemia require regular blood transfusion to prevent complications such as chronic anemia and bone changes.⁴ The ineffective erythropoiesis and increase in the number of multiple blood transfusions in these thalassemic patients lead to iron accumulation.⁵ Deposits of iron initially

GLYCEMIC ABNORMALITIES IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS.

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ABSTRACT... Objectives: The objective of this study was to determine the frequency of glycemic abnormalities i.e. Diabetes Mellitus and Impaired Fasting Glucose in Transfusion Dependent Thalassemia patients. **Study Design:** Cross Sectional study. **Setting:** Center for Thalassemia Care and Patho-Care Laboratory Rahim Yar Khan, Pakistan. **Period:** 6 Months from July 2018 to December 2018. **Material & Methods:** Convenient sampling technique was used. Patients of Transfusion Dependent Thalassemia bearing age more than 10 years were studied. Fasting Plasma Glucose was determined by taking Fasting Blood samples of 151 patients of Transfusion Dependent Thalassemia. A questionnaire was designed and all data collected was recorded. SPSS version 20 used to analyze the data. **Results:** 151 patients were included in the study; 39.1% females and 60.9 % males. Overall 2.0 % patients were found to have Diabetes Mellitus while 4.6% had Impaired Fasting Glucose. **Conclusions:** The results of this study indicated that frequency of Impaired Fasting Glucose is higher as compared to Diabetes Mellitus in Transfusion Dependent Thalassemia patients.

Key words: Diabetes Mellitus, Glycemic Abnormalities, Impaired Fasting Glucose, Thalassemia.

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refer to the storage of iron in the form of ferritin and hemosiderin in reticuloendothelial cells of the spleen, liver and bone marrow^{6,7}, followed by endocrine glands and hepatocytes which result in endocrine complications. The most significant endocrine problem is diabetes mellitus which is considered the most important metabolic disease in humans though dwarfism, hypogonadism, hypothyroidism are also the complications of iron overload.⁸ In patients with transfusion dependent thalassemia disturbed glucose homeostasis results in increased resistance to glucose intolerance and obvious diabetes mellitus.⁹

In addition, pancreatic cells have high divalent metal transporter expression that further improves iron accumulation in these cells, followed by cell apoptosis, pancreatic volume reduction, fat replacement and pancreatic dysfunction.¹⁰ Insulin resistance and insulin deficiency mark both impaired fasting glycemia (pre-diabetic condition) and diabetes mellitus.¹¹ Impaired

fasting plasma glucose is a state in which fasting glucose is above normal but is not high enough to be classified as diabetes mellitus.¹² Glycemic disorders are so dangerous for thalassemic children that a higher incidence of cardiac complications and heart failure in these patients is associated with diabetes mellitus.⁹ In fact, regardless of the use of iron chelation therapy in patients with thalassemia, diabetes mellitus may lead to continuous organic dysfunction.¹³

The most commonly used screening tools for diabetes mellitus are the oral glucose tolerance test (OGTT) and glycosylated hemoglobin (HbA1c) (HbA1C) that have been shown to be beneficial for obese individuals and persons having family history of diabetes mellitus. The use of HbA1c is limited in patients with thalassemia patients with thalassemia because hemoglobinopathies and transfusions interfere with HbA1c analysis. The results may be falsely increased or decreased depending on the proximity of the transfusion, the shorter erythrocyte shelf life and the assay used.^{14,15} Because of these limitations, the oral glucose tolerance test (OGTT) has been proposed as the recommended screening method for glycemic abnormalities in patients with thalassemia.¹⁶

In present study, we determined the frequency of glycemic abnormalities i.e. Diabetes Mellitus and Impaired Fasting Glucose in patients registered in Center for Thalassemia Care at Sheikh Zayed Medical College/ Hospital of Rahim Yar Khan.

The objective of this study was to determine the frequency of glycemic abnormalities i.e. Diabetes Mellitus and Impaired Fasting Glucose (IFG) in Transfusion Dependent Thalassemia patients.

MATERIAL & METHODS

It was cross sectional study conducted at Center for Thalassaemia Care and Patho-Care Laboratory Rahim Yar Khan, Pakistan.

The Study was done in 6 months from July to December 2018.

Sample size was 151 and It was convenient sampling. Only known patients of Transfusion Dependent Thalassemia bearing age greater than 10 years were included in this study.

MATERIALS & METHODS

Fasting Plasma Glucose (FPG) was determined using fasting blood samples of 151 Transfusion Dependent Thalassemia patients. Patients who had FPG greater than 126 mg/dl and 2-Hour Plasma Glucose \geq 200 mg/dl were regarded as Diabetics. FPG level of 100-125 mg/dl and 2-Hours Plasma Glucose, in the 75-g OGTT, between 140 mg/dl were regarded as Impaired Fasting Glucose and normal level of FPG was regarded as 100mg/dl observing Canadian Diabetes Association Clinical Practice Guidelines. Serum Ferritin level was also performed.

The Data was collected by using a pretested Questionnaire. Informed Verbal Consent was taken from attendant of every study subject. The variables included in questionnaire were; Age, Gender, Cast, Ethnicity, Hemoglobin (Hb), Serum Ferritin level, Total Number of Blood Transfusions, Fasting Plasma Glucose, Oral Glucose Tolerance Test (OGTT).

Data analysis was done by using SPSS Version 20.

RESULTS

Figure-1 shows that 92 (60.9 %) Transfusion Dependent Thalassemia patients were males. Mean \pm SD of Age (years) was 13.32 ± 2.08 .

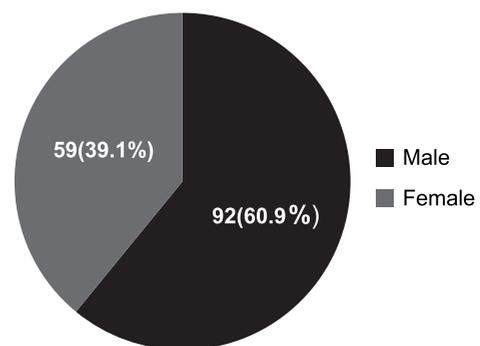


Figure-1. Gender distribution of the transfusion dependent thalassemia patients.

It shows that 6 (85.7%) patients with Impaired fasting plasma glucose and 2 (66.7 %) with Diabetes had no family history of diabetes.

This table shows that 6 (6.5%) male patients with Hyper Ferritinemia had Impaired Fasting Glucose and 3 (3.2%) had Diabetes while 1 (1.7%) Female patient with Hyper Ferritinemia had Impaired Fasting Plasma Glucose.

This table shows that 6 (85.7%) patients with Impaired Fasting Glucose and 1 (33.4%) with Diabetes were 11-14 years of age while 1 (33.4%)

with Impaired Fasting Glucose and 2 (66.7%) with Diabetes were 15-18 years of age.

This shows that 6 (85.7%) patients with Impaired Fasting Glucose and 2 (66.7%) with Diabetes have start of Transfusion within 1-6 months of age while 4 (57.1%) patients with Impaired Fasting Glucose and 2 (66.7%) with Diabetes received total Transfusions within range of 201-400.

This shows that Mean \pm SD of serum Ferritin was 6.468 ± 1.495 .

Glycemic Abnormalities					P-Value
		Normal	Impaired Fasting Glucose	Diabetes Mellitis	
Family History of Diabetes	No	138 (97.8%)	6 (85.7%)	2 (66.7%)	0.03
	Yes	3 (2.13%)	1(1.43%)	1 (33.4%)	

Table-I. Glycemic abnormalities in patients considering to the family history of diabetes.

Serum Ferritin (ng/ml)	Glycemic Abnormalities			P-Value
	Normal	Impaired Fasting Glucose	Diabetes Mellitis	
Hyper Ferritinemia for Males >336	84 (91.3%)	6 (6.5%)	3 (3.2%)	0.15
Hyper Ferritinemia for Females > 306	57 (96.6%)	1 (1.7%)	0 (0%)	

Table-II. Correlation of serum ferritin and glycemic abnormalities in study subjects (n=151)

		Glycemic Abnormalities			P-Value
		Normal	Impaired Fasting Glucose	Diabetes Mellitis	
Age in Years	11-14	97 (68.78)	6 (85.7%)	1 (33.4%)	0.5
	15-18	40 (29.07%)	1 (14.3%)	2 (66.7%)	
	19-22	4(2.83%)	0	0	

Table-III. Fasting plasma glucose according to Age of study subjects (n=151).

Variables		Glycemic Abnormalities			P-Value
		Normal	Impaired Fasting Glucose	Diabetes Mellitis	
Age of First Transfusion	\leq 6 Months	102 (72.3%)	6 (85.7%)	2 (66.7%)	0.01
	7-12 Months	36 (25.53%)	1 (14.3%)	0	
	13-18 Months	3 (2.1%)	0	1 (33.4%)	
Total Number of Transfusions	1-200	18 (12.7%)	1 (14.3%)	0	0.8
	201-400	100 (70.9%)	4 (57.1%)	2 (66.7%)	
	401-600	23 (16.3%)	2 (28.6%)	1 (33.4%)	

Table-IV. Representation of glycemic abnormalities with transfusion variables.

Statistics	Mean \pm SD
Age of First Transfusion	5.47 \pm 2.830
Total Number of Transfusions	308.09 \pm 105.447
Hemoglobin (Hb)	6.468 \pm 1.495
Serum Ferritin	2636.432 \pm 1394.027

Table-V. Statistics of quantitative variables in study subjects (n=151).

DISCUSSION

Diabetes Mellitus is one of the serious complications in Transfusion Dependent Thalassemia patients. Its morbidity and mortality is increasing in these patients. This study was done to assess the frequency of Diabetes Mellitus and Impaired Fasting Glucose in Transfusion Dependent Thalassemia patients. The study involved total of 151 patients Transfusion Dependent Thalassemia patients of age greater than 10 years. This study showed that frequency of Diabetes in Transfusion Dependent Thalassemia patients was 2.0%. A study conducted in Iran showed that frequency of Diabetes in Transfusion Dependent Thalassemia Irani patients was 8.8%.¹⁷ Diabetes Mellitus has also been reported with frequencies of 10.5% in United Arab Emirates,^{17,18} 6% in Saudi Arabia, 9.4% in Brazil¹⁹, 18.6% in United States of America²⁰, and 41% in United Kingdom.²¹ In present study frequency of Impaired Fasting Glucose was 4.6 %. However other studies showed this frequency as 12.9 % in Iran. In a review study the prevalence of Impaired Fasting Glucose in adult patients of Iran has been reported as 16.8 % and it also showed that with increasing age the prevalence was increasing.²² Genetic, geographical, cultural and economic factors as well as the quality of blood transfusion and chelation therapy result in frequency difference of Diabetes and Impaired Fasting Plasma Glucose in various countries.²³ The mean age of Thalassemic patients in present study was 13.32 ± 2.08 years with the age distribution ranging between eleven to twenty years. Current study population had a relatively younger age group when compared to other studies as the study conducted in Iran mean age was 17.3 ± 6.7 with ranges of ten to forty years. In another study in Iran the mean age was 19.6 ± 4.4 years.¹⁷ The mean age of onset of diabetes, assessed in a large set of cases in Italy, was 18.1 years. A study also reported also reported the onset of diabetes to occur after 18 years of age.²⁴ Present study revealed a significant relationship between the Age of first transfusion and Fasting Plasma Glucose with P value of 0.01. In this study Mean \pm SD of Age of first Transfusion is 5.47 ± 2.83 . However in other studies this relationship was not found. All the Thalassemic patients in current study had iron overload and raised serum

Ferritin, however there is no significant association was found between serum Ferritin and Fasting Glucose levels in present study with a p-value of 0.1. Similar to present study the study conducted in Indonesia showed no correlation between serum Ferritin and Fasting Glucose levels.²⁵ This fact might be due to the high reserve in pancreatic endocrine function in the study population. Therefore, although an increase in ferritin level occurred, the pancreas is able to secrete enough insulin. However Pancreatic function was not assessed in Thalassemic patients in present study. In contrast to current study a significant correlation was found in serum Ferritin and Fasting Glucose in the study conducted in Iran however in this study we found a significant relationship between fasting glucose and severity of hyperferritinemia that had a P value of 0.00.¹⁷ In present study majority of patients with Impaired Fasting Glucose and Diabetes Mellitus had serum Ferritin between the range of 2001 to 2004 (2001-4000 ng/ml). In present study a significant relationship was found between the family history of Diabetes and frequency of Impaired Fasting Glucose and Diabetes Mellitus indicated by a P value of 0.03. In contrast to our study a study conducted in Indonesia showed no relationship.²⁶

CONCLUSION

It has been concluded that the frequency of Impaired Fasting Glucose is higher as compared to Diabetes Mellitus in Transfusion Dependent Thalassemia patients. It has been revealed in current study that age of first transfusion and family history of Diabetes Mellitus are strongly associated risk factors for development of Diabetes Mellitus and Impaired Fasting Glucose. Therefore, screening for the early diagnosis of this endocrine complication in every six month should be done to improve the quality life of these patients.

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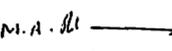
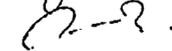
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Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
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2	M. Shahbaz Hussain	Data collection & literature review.	
3	M. Abdul Rehman	Critical review & Data analysis.	M. A. Rehman 
4	Mazhar Hussain	Manuscript writing and analysis.	
5	M. Ali Malik	Data collection, Discussion.	
6	Ghulam Mustafa	Static analysis + Proof reading.	