

Diabetes Mellitus in Multitransfused Thalassaemia Patients at Sir Ganga Ram Hospital, Lahore

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ABSTRACT

Objective: To determine diabetes mellitus in multitransfused thalassaemia patients and its relationship with iron overload at Sir Ganga Ram Hospital, Lahore.

Method: A cross-sectional study was conducted among thalassaemia patients, at the Thalassaemia Centre, Paediatric Department, Sir Ganga Ram Hospital, Lahore. A structured questionnaire was used to collect information. The children included in the study were more than ten years of age and had multiple blood transfusions. All patients underwent a standardized glucose tolerance test (GTT). SPSS 17.0 was used for data entry and analysis.

Results: A total of 107 thalassaemia patients participated in the study, 65 were males and 42 were females with age ranges of 10 – 30yrs(mean 15yrs). and the average BMI was 16. The mean time of diagnosis was 1.32yrs. The average age of having first blood transfusion was 3yrs. Iron chelation was started at an average of 7.58yrs; where as 95.3% of patients were using both iron chelation along with regular blood transfusions. The mean value for serum ferritin was 5671ng/ml and average pre-transfusion haemoglobin was 7.48gm. There were 4 cases of diabetes mellitus; out of which 3 had a significant family history of the disease. Nine (8.4%) of cases had an impaired glucose tolerance test. There was a significant association with fasting blood sugar, 2 hour GTT readings and serum ferritin levels (Fisher's Exact Test p-value of 0.045 and 0.024 respectively).

Conclusion: The children with higher levels of ferritin were at a greater risk of developing endocrine dysfunction of the pancreas but family history of diabetes posed a greater risk of overt diabetes with elevated levels of ferritin. It is therefore recommended that iron chelation therapy be initiated earlier and especially in those having a strong family history of diabetes. Periodic screening for impaired glucose tolerance can help to identify and initiate timely appropriate interventions.

INTRODUCTION

Thalassaemia major (b-thalassaemia) is one of the commonest inherited disorders in Pakistan. The carrier frequency varies from 4 - 5 percent in different parts and ethnic groups of the country.^{1,2} It is estimated that nearly 4000-5000 thalassaemia major children are born in Pakistan every year.^{3,4}

These patients need regular blood transfusions and thus iron overload may develop in many organs including liver, heart and endocrine glands. Iron overload in the pancreas may result in impaired glucose tolerance and lead to frank diabetes mellitus. This dreaded complication in thalassaemic children may confront them to deal with two chronic illnesses, having both physical and economic implications particularly in patients from lower socio-economic group.

The normal individuals with family history of diabetes mellitus may have a higher risk of developing the disease. If one parent is suffering from diabetes then the risk of the offspring (< 50yrs of age) of developing the disease is 1 in 7.⁵ In thalassaemia patients due to the massive iron overload due to breakdown of RBCs they are at a

higher risk of developing pancreatic dysfunction (ref). The present study is aimed at to identify the frequency of diabetes mellitus in multi-transfused thalassaemic patients.

METHODS

This study was conducted at the Thalassaemia center, Paediatric Unit of Sir Ganga Ram Hospital, Lahore. The study span was from 1st September 2010 to 1st November 2010. Our study comprised of 107 patients over ten years of age diagnosed with beta thalassaemia visiting the outpatient department with regular follow-up. Patients with any acute illness were excluded from study. The study subjects were enrolled by non-probability sampling (convenient). Informed consent was taken from the patients / guardians and data was collected with the help of a structured questionnaire. Blood samples for Serum Ferritin level were sent for evaluation to a reference laboratory, in addition to standardized Glucose tolerance test were done at main clinical Laboratory of Sir Ganga Ram Hospital. SPSS version 17.0 was used for data entry and analysis.

Initial analysis included frequency distribution for categorical variables and Chi-square test or Fisher's exact test was used to document statistical significance between categorical variables.

RESULTS

A total of 107 thalassemia patients from the thalassemia centre of Sir Ganga Ram hospital, Lahore participated in the study. Table 1 shows the demographic characteristics of the study participants. In this study, 64 male and 43 female patients were enrolled. Seventy five percent of the

cases were aged between 11 to 20 years and the average age of the patients, was 15 years. Majority of the cases (57.9%) belonged to lower socioeconomic class based on their family income, followed by middle (38.3%) and upper socioeconomic group (3.7%) . The average monthly income was 10740 rupees. About (62%) cases were living in the urban (29%) in the rural and 9.3% in semi urban areas. Only 51% of the patients were literate. Thirty nine percent of fathers had education upto matriculation, whereas; 50% of the mothers were illiterate.

Table 1: Serum Glucose level (GTT Fasting) compared with Serum Ferritin Levels among thalassaemia patients

	Serum Ferritin Level (ng/ml)				
	<1000 (ng/ml) (n=1)	1000 – 2500 (ng/ml) (n=9)	2600 – 4000 (ng/ml) (N=26)	>4000 (ng/ml) (N=71)	
Serum Glucose (Fasting)					
Normal	1	6	26	66	99
Impaired	0	1	0	4	5
Diabetic	0	2	0	1	3
P-value = 0.045					

Table 2: Serum Glucose Level (GTT After 2 hours) by Serum Ferritin among Thalassemia Patients

	Serum Ferritin Level (ng/ml)				
	<1000 (ng/ml) (n=1)	1000 – 2500 (ng/ml) (n=9)	2600 – 4000 (ng/ml) (N=26)	>4000 (ng/ml) (N=71)	
Serum Glucose (Fasting)					
Normal	1	7	22	66	96
Impaired	0	0	4	5	9
Diabetic	0	2	0	0	2
P-value = 0.024					

The average age at the time of diagnosis was 1.32 years. Most of cases (64.4%) had started blood transfusion therapy at the age of less than three years. The average age at the start of iron chelation therapy was 7.58 years. Almost all of the cases (97.2%) were seen on outpatient basis, and only (2.8%) came through emergency. Majority (79.4%) had thalassemia major; (95.3%) were receiving both blood transfusion and chelation

therapy, and very few (4.7%) were receiving only blood transfusion therapy. The most common iron chelating agent used by the patient was desferioxamine (44.9%), (28.1%) were receiving desferioxamine and deferiprone (ferrinil), 12.1% were using desferioxamine and deferasirox, and (10.3%) were using deferasirox. About (61.7%) of the cases were taking chelation therapy regularly.

The average serum ferritin level of the cases was 5671.42 (ng/ml), and average serum haemoglobin prior to blood transfusion was 7.48 gm. Mean serum glucose (GTT fasting) and serum glucose (GTT 2 hrs) of the patient were 80.90 and 102.32 mg/dl respectively. Only a few (9.3%) of the cases had family history for diabetes mellitus (DM). Presence of DM was reported in only (3.7%) of the cases, while three out of four patients had diabetes with positive family history of DM, (1.9%) had type I DM and (1.9%) had type II DM; (0.9%) had DM since one year, and (1.9%) had DM for last two years.

The mean serum glucose (GTT fasting) values of the patients were (75.00 mg/dl), (90.33mg/dl), (79.35mg/dl), and (80.37mg/dl) and the mean serum glucose (GTT after 2 hrs) values of the patients were (83.00mg/dl), (129.44mg/dl), (102.27mg/dl), and (99.18mg/dl) with serum ferritin levels (<1000 ng/ml), (1000- 2500 ng/ml), (2600 – 4000 ng/ml), and (>4000 ng/ml) respectively.

Fisher's Exact test showed that serum glucose (GTT fasting) was significantly associated with serum ferritin (p-value = 0.045). Of the cases with normal GTT majority (66) had serum ferritin greater than 4000 ng/dl. Of the 5 cases with impaired GTT (fasting), 4 had serum ferritin greater than 4000 ng/dl, whereas, one had serum ferritin level between 1000 to 2500ng/dl. Three of the cases were diabetic based on GTT (fasting), of whom 2 had serum ferritin between 1000 to 2500 ng/dl and 1 had greater than 4000ng/dl serum ferritin level.

Serum glucose (GTT 2 hrs) was also found to be significantly associated with serum ferritin (p-value = 0.024). Out of 96 cases with normal (GTT 2 hrs) majority (66) had serum ferritin greater than 4000 ng/dl, twenty two had serum ferritin between 2600 to 4000 ng/dl, (7) had serum ferritin between 1000-2500 ng/dl, and one had serum ferritin less than 1000 ng/dl. Of the nine cases with impaired (GTT 2 hrs), five had serum ferritin greater than 4000 ng/dl, and four had serum ferritin between 2600 to 4000 ng/dl. Only two cases had diabetic GTT after 2 hrs and serum ferritin 1000 to 2500 ng/dl.

DISCUSSION

Thalassaemia is one of the major public health problems in Pakistan. In the study done by Satwani et al it was reported, that in Pakistan, there are about 8-10 million thalassaemia carriers. In the present study, our results had showed that

starting time for iron chelation therapy was very late. Iron chelation appeared insufficient in our study population. Poor compliance to blood transfusion and late start of chelation therapy has markedly reduced the life expectancy in our patients as compared to western population. Sachdeva et al, also found the similar mean age of onset of chelation in their study group. Gamberini MR et al also reported, that the main risk factors associated with insulin dependent DM were poor compliance with desferioxamine treatment, advanced age at the start of intensive chelation therapy.

Guidelines from Thalassaemia International Federation recommend that chelation therapy should be initiated when serum ferritin level is raised approximately upto 1000 ng/ml. For patients requiring regular blood transfusions, iron chelation may represent life-saving therapy.

In the present study, the over all mean serum ferritin level was 5671.42 ng/ml, almost all of the patients (95.3%) were receiving both blood transfusion and chelation therapy. Hence about 62% patients could be considered to be taking adequate chelation therapy. The mean serum hemoglobin level of the patient was 7.5g/dl.

A study conducted by Olivieri NF demonstrated that, Iron overload of tissues, which is fatal with or without transfusion, if not prevented or adequately treated, may result is the most important complication of beta thalassaemia and is a major focus of management. In another study. In Ong CK et al study, iron chelation appeared insufficient as the prevalence of DM reported was 8%.

A study by Matter RM assessed that, thalassaemic patients with abnormal glucose tolerance; including diabetics and thalassaemics with impaired glucose; displayed a higher degree of pancreatic and hepatic siderosis compared to thalassaemics with normal glucose tolerance. Hafez M et al observed abnormal glucose tolerance in (24.1%) of the patients. Najafipour F et al found DM in (8.9%), impaired fasting glucose in (28.6%), and an impaired glucose tolerance in 7.1% patients. In another study by Mehrvar A et al, (5.4%) of the patients suffered from diabetes. Hatunic M et al found (13%) of the patients had DM, and (15%) had impaired glucose tolerance.

In our study a significant association was observed between serum glucose levels (GTT fasting) and serum ferritin levels (P value = 0.045). Also a similar significant association was observed between serum glucose levels (GTT after 2 hrs)

and serum ferritin levels (P value =0.024). Similar significant results were reported by Acton RT et al. In this study, the over all prevalence of diabetes was (13.8%).

According to Ford ES et al study, elevated serum ferritin concentration was associated with an increased risk of diabetes. All multiple linear regression coefficients between ferritin levels and glucose were positive for both men and women.

In our study, 10 subjects (9.3%) had positive family history of diabetes in a first and second degree. Of the 4(3.7%) subjects had DM, of whom 3(75%) had positive family history for the DM. Sschdeva A et al in their study was found positive family history of diabetes in (47%) of the subjects. In a study done by Jimmy et al and Chern et al the prevalence of impaired glucose tolerance was 8.5 % and that of diabetes were 19.5%. The risk factors for abnormal glucose tolerance were serum ferritin concentration. Family history was not a risk factor.

In a study done by Christopher D et al glucose intolerance was correlated significantly with number of transfusions received, while a positive family history for DM was more common in the subjects with glucose intolerance. In another study, conducted by Sun L et al, elevated circulating ferritin concentrations were found to be associated with higher risk of type II diabetes. Although, we saw that DM presented in patients with varied ranges of ferritin, this can be explained by the fact that some patients have a genetic predisposition for iron loading of the pancreas.

In our study it was found that, majority (83.1%) parents of the patients were illiterate, and hence forth the patients (48.6%). This might be due to illiteracy, reduced awareness about the utilization of the chelation therapy, low socio-economic status, and affordability of the chelation therapy, besides the universal factors of lack of knowledge and poverty. Iron chelation therapy be started earlier and this will help prevent a serious complication of DM in thalassemia patients.

CONCLUSION

Thalassaemic patients with higher levels of ferritin were at a greater risk of developing endocrine dysfunction of the pancreas, but those with a significant family history were at a much higher risk of developing frank diabetes with elevated levels of ferritin. It is recommended that iron chelation therapy be initiated earlier and especially in those who have a strong family history of diabetes.

Periodic screening for impaired glucose tolerance should be done to identify those at risk and initiate appropriate interventions earlier.

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