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March 2012

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## Recommended Citation

Adil, A., Sobani, Z., Jabbar, A., Adil, S., Awan, S. (2012). Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. *Journal of the Pakistan Medical Association*, 62(3), 307-10.

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## **Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan**

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### **Abstract**

**Objective:** To determine the major endocrine complications present in patients of Thalassemia major presenting to a tertiary care center in Karachi, Pakistan.

**Methods:** Records of all thalassemia major patients at a Haematology Department in a tertiary care hospital of Karachi were retrospectively reviewed from May to August 2009 with specific focus on endocrine data and investigations. The patients' data was recorded in a questionnaire and analyzed using SPSS v.17, frequencies and percentages along with corresponding 95% confidence interval were computed.

**Results:** Our data revealed that a significantly small percentage of those under care received regular endocrine follow-up. Male hypo-gonadal abnormalities had the highest probability; 100% of the tested patients had decreased levels of testosterone, while 95.2% had raised serum creatinine levels. Parathyroid dysfunction was noted in 40% of the patients. Of those screened 29.4% had blood glucose levels in the diabetic range and 11.8% of the tested patients had reduced levels of FT4.

**Conclusion:** A high frequency at endocrine dysfunctions seen in thalassaemia patients included: male hypogonadism, parathyroid dysfunction, deranged blood glucose and FT4 levels.

**Keywords:** Thalassaemia, Endocrine disorders, Serum ferritin (JPMA 62:307; 2012).

### **Introduction**

People estimated to be suffering from thalassemia in Pakistan are 70,000, and 6000 new cases of thalassemia present for treatment each year.<sup>1</sup> In Italy 50% of thalassemic patients were estimated to have died before the age of 12 years in the late 1970's.<sup>2</sup> Cornell Medical Center reported a median survival of 17.1 years in patients followed from 1960 to 1976.<sup>3</sup> The advent of safe transfusions has drastically prolonged the life of these patients.<sup>4</sup> But this hope brought with it various complications of repeated transfusions and iron overload.<sup>5</sup>

Studies conducted have shown that these individuals experience various endocrine complications including short stature, hypo-gonadism, hypothyroidism, hypo-parathyroidism, diabetes, and impaired glucose tolerance.<sup>6,7</sup> A recent study states that the age and transfusion periods are risk factors for developing diabetes and that the amount of transfusion is directly linked to impaired fasting glucose levels.<sup>4</sup>

Our Study aims to determine the major endocrine complications of Thalassemia major occurring in a tertiary care center in Karachi, Pakistan, enabling physicians to prioritize the endocrine complications occurring in the population and

test accordingly where financial constraints may limit comprehensive screening. In thalassemic patients a common finding is elevated ferritin levels and some studies have shown a relationship between survival and endocrine problems in thalassemic patients using serum ferritin as a prognostic marker.<sup>8,9</sup> We also aim to investigate if it is feasible to use ferritin as prognostic marker in our thalassemic population.

### **Patients and Methods**

The study was carried out retrospectively. Medical students reviewed the records of all thalassemia major patients under regular care of the Department of Haematology, and those receiving regular blood transfusions at our day care facility. An updated list of patients was obtained from the transfusion center of the hospital till February 2009. Since the university hospital receives patients from diverse social and financial backgrounds from all over the country, the study participants were projected to be a representative sample of the population.

The files were reviewed from May to August 2009 with specific focus on endocrine data and investigations of the patients and the data was recorded in a questionnaire. In cases where repeated investigations were performed the most recent levels were considered in analysis; however

data was excluded if specific replacement therapy or medication was employed (e.g. Testosterone levels in a patient undergoing hormone replacement therapy was not included in the analysis.). The specific tests run to calculate different lab values have been mentioned in Table-1. Reference values were considered low or high according to the normal ranges published by the Aga Khan University Hospital laboratory.

The data was analyzed using SPSS v.16, frequencies and percentages along with corresponding 95% confidence interval were computed. Our analysis evaluated the percentage of patients receiving a specific endocrine test and the percentage of those with abnormalities; calculating the probability of abnormal findings on a specific test. The height, weight and BMI of patients were analyzed to check for any discrepancy. Relation between increased ferritin and the endocrine findings was also investigated.

## Results

Primary analysis of our data revealed that a significantly small percentage of those under care received regular endocrine follow-up. Of the 124 patients included in the study 68 (54.8%) were male and 56 (45.2%) were female, with an average age of  $12 \pm 8$  years. As indicated in table 1. Male hypo-gonadal abnormalities had the highest probability as 100%. Of the tested, 13.2% patients had decreased levels of total testosterone. Of the tested 67.7% patients, 95.2% (CI= 90.7-99.8) had raised serum creatinine levels. The patients also showed elevated liver function

tests. The mean serum alkaline phosphatase level was elevated in 47.1% of the patients. Whereas 46.4% of the 90.3% who had their SGPT levels tested also showed elevated values; indicating that some level of subclinical liver damage may be present in approximately 46% of the patient population. FT4 level in 11.8% of the tested 27.4% of patients was reduced; however of the tested 21.6% of patients all had TSH levels within normal ranges. Parathyroid dysfunction was also noted in 40% of the 8.1% tested; coinciding with the 35.3% (41.1% tested) having impaired calcium and 43.3% (24.2% tested) having impaired phosphate levels. Patients screened for diabetes were 13.7% (Fasting Blood Glucose > 26) out of which 29.4% had values in the diabetic range and none of them were in the impaired fasting glucose range (110 - 126). Serum cortisol levels were also checked in 5.6% patients out of which 28.6% had lower than normal values.

We divided the Ferritin levels into four quartiles, with four groups, each having ranges between, 764-2516, 2517-4055, 4056-6385 and 6386-14184 (Table-2). The lab values i.e. FT4, FBS, Ca, Phosphate, Alkaline phosphatase, PTH, testosterone, SGPT and creatinine were correlated with Ferritin levels to determine whether an association was present. The data showed increasing serum ferritin levels within increased incidence of some abnormal laboratory values. Increasing ferritin levels showed a subsequent increase in the serum levels of parathyroid hormone (PTH) and a subsequent rise in calcium (Ca), SGPT and alkaline phosphatase.

**Table-1: Summary of endocrine tests performed with probability of abnormal findings.**

	Normal values	Total number of patients tested	Number of patients with abnormal findings	Percentage of patients with abnormal findings	Confidence interval	Test method
FT4	0.93-1.7	34	4	11.8%	0.9-22.6	Electrochemo luminescence
FBS	65-110	17	5	29.4%	7.8-51.1	
RBS	80-160	31	11	35.5%	18.6-52.3	Glucose oxidase
Ca	8.6-10.5	51	18	35.3%	22.2-48.4	Ion selective electrode (ISE)
Phosphate	4.4-6.0	30	13	43.3%	25.6-61.1	Time endpoint
Alk. Phosphate	125-405	51	24	47.1%	33.4-60.8	Kinetic rate
PTH	16-87	10	4	40%	9.6-70.4	chemo luminescence
Total Testosterone	below	9	9	100%		Electrochemo luminescence
SGPT	0-55	112	52	46.4%	37.2-55.7	Kinetic rate
Creatinine	0.85-1.35	84	80	95.2%	90.7-99.8	Modified jafferate
Sr Cortisol	below	7	2	28.6%	-4.9-62	Flourscent smthg Immuno assay FPIA
TSH	below	33	0	0%		Electrochemo luminescence

### Testosterone reference ranges:

	Adult Males	Adult Females
20-49 Years	249-836	8.4-48.1
>50 Years	193-740	2.9-40.8
	Boys	Girls
1-5 Years	2-25	2-10
6-9 Years	3-30	2-20
Pubertal		
10-19 Years	2-800	2-40

### Cortisol reference ranges:

AM	4.2 - 38.4
PM	1.7 - 16.6
TSH reference ranges	
Age	Range uIU/ml
21 weeks-20 years	0.7--6.4
Adults	
21-54 Years	0.4--4.2
55-87 Years	0.5--8.9

**Table-2: Relationship between abnormal findings and ferritin levels.**

	Ferritin (764-2516) n=29 (25.2)	Ferritin (2517-4055) n=29 (25.2)	Ferritin (4056-6385) n=29 (25.2)	Ferritin (6386-14184) n=28 (24.3)
↓ FT4	0(100%)	1/6(17%)	2/11(19%)	1/13(8%)
↑ FBS	0(0%)	1/3(34%)	1/7(14.2%)	2/4(50%)
↑ Ca	3/9(33.3)	3/12(25%)	5/14(36%)	6/14(43%)
↑ Phosphate	3/3(100%)	2/7(29%)	4/10(40%)	4/9(45%)
↑ Alk. Phosphate	4/14(29%)	6/12(50%)	7/10(70%)	6/13(46.1%)
↑ PTH	0(0%)	0(0%)	2/6(34%)	2/3(67%)
↑ Testosterone	1/1(100%)	1/1(100%)	3/3(100%)	4/4(100%)
↑ SGPT	10/24(42%)	9/28(32%)	12/29(42%)	20/28(71.4%)
↑ Creatinine	21/21(100%)	18/18(100%)	21/22(95%)	17/20(85%)

## Discussion

Beta-thalassemia represents a group of recessively inherited haemoglobin disorders, first described by Cooley and Lee,<sup>10</sup> characterized by reduced synthesis of  $\beta$ -globin chains leading to synthesis of haemoglobin with an impaired oxygen binding capacity. The homozygous state, known as beta-thalassemia major, results in a severe haemolytic anaemia requiring regular blood transfusions.<sup>11</sup> The advent of safe transfusions with adjuvant chelation therapy has dramatically extended the life expectancy of thalassaemic patients, who can now survive into their fourth and fifth decades of life.<sup>11</sup> However, frequent blood transfusions have been associated with serum iron overload, which may result in hypo-gonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and other endocrine abnormalities.<sup>12</sup>

Growth retardation is frequently profound in these children, maybe attributable to the diversion of caloric resources toward ineffective erythropoiesis, along with the effects of anaemia, since hyper-transfusion has been shown to frequently restore normal growth rates.<sup>13</sup> However, the adolescent growth spurt is often delayed, even in children who are hyper-transfused, unless intensive iron chelation therapy is instituted early in life.<sup>14</sup> Studies have also attributed the decreased growth to iron overload, the toxic effects of desferrioxamine, or the development of other endocrinopathies such as growth hormone insufficiency or primary hypothyroidism.<sup>15</sup> Thus, normal stature is rarely attained, even in well-managed patients. Growth failure was not as frequent in our sample as compared to other studies; 77.4% of our patients had normal BMIs, while 4.8% were overweight and 6.5% were categorized as obese.

Hypo-parathyroidism is thought to be a rare complication of beta-thalassemia major that is usually but not always accompanied by hypo-calcaemia.<sup>16</sup> It may also be associated with various neurological manifestations, including tetany, seizures, carpopedal spasms and paresthaesia, and little is known about these associated complications in thalassaemic patients.<sup>16</sup> In our study 35.3%

of the participants were found to be hypo-calcaemic where Dresner R. et. al reported that hypo-calcaemia was present in 16.6% of thalassaemic patients,<sup>17</sup> and Gulati et. al reported a prevalence of 13.5% in his study population.<sup>18</sup> Hyper-phosphataemia was associated with 60% of participants who were hypo-calcaemic.

Forty seven percent of our patients had an increased alkaline phosphatase, which may be attributable to vitamin D deficiency (endemic in our population) or liver disease,<sup>10</sup> but in the absence of clinical manifestations of disease process the underlying mechanism in our sample could not be hypothesized.

Thyroid dysfunction has been reported in 9% to 60% of patients with thalassemia,<sup>19,20</sup> but its severity is variable in different series.<sup>21</sup> Hypothyroidism was found in 11.8% of our patients.

A high prevalence of endocrine abnormalities in beta thalassemia major patients is reported by several authors.<sup>23,24</sup> Some studies have reported a relationship between the level of ferritin and the development of endocrinopathies;<sup>8</sup> suggesting the use of serum ferritin as a prognostic marker for survival, it has been reported that the prognosis for survival is excellent for thalassaemic patients with serum ferritin concentration below 2500  $\mu\text{g/l}$ .<sup>9</sup> In contrast other studies report the absence of such a relation.<sup>24</sup>

Our data suggests that increasing serum ferritin levels show increased incidence of some endocrinopathies. Increasing ferritin levels showed a subsequent increase in the serum levels of calcium (Ca), alkaline phosphate (Alk. phosphate) and parathyroid hormone (PTH); however the relationship was not predictive.

Our limited sample size and the fact that it is a single center study restricts the generalization of our results to the entire population.

With the improved survival of thalassaemic patients, and the high incidence of multiple endocrine complications, it is important to carry out endocrine evaluation regularly,

especially in patients with iron overload and poor compliance with chelation therapy. The relatively high frequency of some endocrine dysfunctions found in our study may be attributable to poor disease control or management in early life when irreversible tissue damage occurs due to iron overload, reinforcing the importance of regular evaluation of patients with thalassemia major for early detection and management of associated complications.

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