

# Prevalence of iron overload complications among patients with $\beta$ -thalassemia major treated at Dubai Thalassemia Centre

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**BACKGROUND AND OBJECTIVES:** Authors and team members of the Dubai Thalassemia Centre obtained data on the prevalence of iron overload complications among patients with  $\beta$ -thalassemia major ( $\beta$ -TM) and compared it to international data to improve patient care and evaluate the effectiveness of earlier used treatment modalities. The information obtained is also expected to be useful in genetic counseling.

**DESIGN AND SETTING:** Cross-sectional study of all living transfusion-dependent  $\beta$ -TM patients registered at the Thalassemia Centre in Dubai, United Arab Emirates, until the end of 2007 (n=382).

**PATIENTS AND METHODS:** Diagnosis of TM was based on clinical history and laboratory confirmation by hemoglobin electrophoresis and DNA testing. All were uniformly treated with desferrioxamine and monitored by serial serum ferritin.

**RESULTS:** The mean (SD) age of patients was 15.4 (7.6) years, with 50.5% males. Mean (SD) serum ferritin was 2597.2 (1976.8)  $\mu$ g/L. The frequency of iron overload complications were as follows: hypogonadism (n=99, 52.7%), hypoparathyroidism (n=40, 10.5%), diabetes mellitus (n=40, 10.5%), hypothyroidism (n=24, 6.5%) and cardiomyopathies (n=7, 1.8%). Hypogonadism was the most common endocrine abnormality in our study and other reported series. However, cardiomyopathies were less prevalent among our patients with higher rates of diabetes and hypoparathyroidism compared to rates reported internationally. Females had statistically significant lower serum ferritin (2530.8 (1931.2),  $P<.05$ ) with a lower cardiomyopathies rate.

**CONCLUSION:** Iron overload related complications among our patients with thalassemia major were different from those reported internationally. Studying the genetic status of patients from our area may uncover the underlying genetic modifiers of iron overload mediated organs injury.

In the last 40 years, conventional treatment of  $\beta$ -thalassemia major ( $\beta$ -TM), based primarily on regular blood transfusions and iron chelation therapy with desferrioxamine (DFO) has markedly improved the prognosis of the disease.<sup>1-4</sup> Unfortunately DFO is difficult to administer and hard to comply with, particularly in adolescents and young adults.<sup>5</sup> As a result, patients are at risk of developing complications of hemochromatosis of the cardiac, hepatic and endocrine systems.<sup>6-8</sup>

This retrospective study was conducted at Thalassemia Centre in Dubai to generate baseline data on the prevalence of iron overload complications among patients with  $\beta$ -TM being treated at the cen-

tre prior to the introduction of new oral iron chelators and MRI T2\*. This data was utilized for benchmarking with the internationally reported prevalence. Moreover, it should be of great use in evaluating the impact of the new oral iron chelators and new methods for measuring tissue iron in the future. This is the largest group of patients and the first attempt to compile such data on patients from our area.

## PATIENTS AND METHODS

This was a cross-sectional study of all living transfusion-dependent  $\beta$ -TM patients registered at the Thalassemia Center in Dubai, UAE, until the end of 2007 (n=382). Diagnosis of  $\beta$ -TM was based on a

clinical history and laboratory confirmation by hemoglobin electrophoresis and DNA testing. All our enrolled patients were regularly transfused at 3-4 weeks intervals with the aim of maintaining a pretransfusion hemoglobin concentration of 9-9.5 g/dL and had received long-term subcutaneous DFO infusion at an average dose of 40g/kg/day over 10-12 hours for 5-6 nights per week. Adequate iron chelation was assessed by serial serum ferritin levels. Data recorded included demographics (age, sex and nationality), serum ferritin and endocrine, cardiac and hepatic complications. Age of onset and 2-year average ferritin values for each patient were recorded. Patients had been examined to determine their pubertal status. Hypogonadism was defined as an absence of breast development in girls by the age of 15 years and absence of testicular enlargement in boys by the age of 17 years.<sup>9</sup> Hypothyroidism was defined based on high thyroid stimulating hormone with low FT4. Hypoparathyroidism was diagnosed based on low corrected calcium concentration, high phosphorus and inappropriately low or normal parathyroid hormone levels. Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association (1997).

Results were analyzed by descriptive statistical methods using median, means and standard deviation (SD) or percentages. Pearson partial correlation was used to determine the association of serum ferritin levels and age. A bivariate analysis test was used to determine the correlation between gender and serum ferritin. All

**Table 1.** Demographics of patients with  $\beta$ -thalassemia major at Dubai Thalassemia Centre.

Mean age (years)	15.4 (7.6)
Median age (years)	15
Pediatric (<15 years)	n=177 (46.30%)
Adults ( $\geq$ 15 years)	n=205 (53.70%)
Males	n=193 (50.50%)
Females	n=189 (49.50%)
UAE-National	n=169 (44.20%)
Non UAE	n=213 (55.80%)
Pakistan	n=72 (18.90%)
India	n=26 (6.80%)
Oman	n=49 (12.80%)
Iran	n=19 (5%)
Other Arab countries	n=13 (3.40%)
Others	n=34 (8.90%)

**Table 2.** Iron overload complications among patients with  $\beta$ -Thalassemia major at Dubai Thalassemia Centre.

Complications	No. of patients (%)	Mean age Of onset (years)	Median serum ferritin (ng/mL) <sup>a</sup>
Diabetes Mellitus	40 (10.5)	19 (4.4)	3410
Hypothyroidism	24 (6.5)	18 (4.26)	2668
Hypoparathyroidism	40 (10.5)	18.3 (4.5)	3661
Hypogonadism <sup>b</sup>	99 (52.7)	16.5 (1.9)	2719
Cardiomyopathy <sup>c</sup>	7 (1.8)	21.3 (2.8)	2953

<sup>a</sup>Median for two years serial serum ferritin values prior to complication diagnosis; <sup>b</sup>Only 188 patients were old enough to be assessed for hypogonadism; <sup>c</sup>Heart failure and arrhythmias

**Table 3.** Correlation of serum ferritin with gender among patients with  $\beta$ -thalassemia major at Dubai Thalassemia Centre.

Gender	Serum ferritin	Correlation
Females	2530.8 (1931.2)	0.049 ( $P<.05$ )
Males	2650.8 (2023.3)	0.091 ( $P>.05$ )

$P$  values are two sided with a level of significance set at  $P<.05$ . Analyses were performed using SPSS 12.0 for Windows software.

## RESULTS

The overall population analyzed was 382 patients, of whom 193 (50.5%) were males. The mean age of the studied population was 15.4 (7.6) years (range, 2-37 years) (Table 1). Seventy-six percent of our patients were born after 1985 and 30 patients (7.9%) were splenectomized. The frequency of iron overload complications are shown in Table 2. The mean age of diagnosis for endocrine complications was 18.0 (3.7 years and 21.3 (2.8) years for cardiomyopathies (Table 2). The mean serum ferritin level of the population was 2597.2 (1976.8)  $\mu$ g/L. There was a significantly positive correlation between serum ferritin level and age with poor linearity ( $r=0.416$ ,  $P<.001$ ). Females had a statistically significant low serum ferritin (2530.8 [1931.2],  $P<.05$ ) compared to males (Table 3).

## DISCUSSION

Detection of large international differences in rates for other diseases has been important in both assessing the relative magnitude of disease burden between countries and in stimulating new research efforts to understand both disease etiology and prevention.<sup>10</sup> In the present cross-sectional study, we found a considerable endocrinopathies in our population. Hypogonadism was the most common endocrine abnormality in our study and

**Table 4.** Benchmarking with other studies.

Patient Data	Dubai	Hong Kong <sup>10</sup>	North America <sup>12</sup>	Italy <sup>24</sup>	Iran <sup>11</sup>	Saudi Arabia <sup>23</sup>	Lebanon <sup>27</sup>
Mean age (years)	15.4 (7.6)	-	-	-	-	13.6	-
Median age (years)	15	15.5	20	-	15.2	-	-
Male%: Female%	50.5:49.5	50.8:49.2	-	53.3:46.7	51.5:48.5	-	-
Median serum ferritin (ng/mL)	1943	2260.3	1710	-	-	-	-

other reported series. However, the cardiomyopathy rate was low (1.8%) with high diabetes (10.5%) and hypoparathyroidism (10.5%) compared to those reported internationally (Table 4). The discrepancy in complication rates cannot be attributed to simply age or serum ferritin difference. Our population had comparable median age (15 years) to both Hong Kong (15.5 years) and Iranian (15.2 years) cohorts, although they had a lower median age compared to North America cohorts (20 years).<sup>11-13</sup> Moreover our patients had higher median serum ferritin (1943 ng/mL) compared to a North America cohort (1710 ng/mL).<sup>13</sup>

Iron overload cardiomyopathies (IOC) among our patients were associated with 2-year median serum ferritin prior to diagnosis of 2953 ng/mL, which is consistent with earlier reports stating that transfused patients with serum ferritin concentrations below 2500 ng/mL had a better prognosis for survival without cardiac disease.<sup>2</sup> Cardiomyopathies were not reported in our patients less than 15 years of age, which was similar to a North American report.<sup>13</sup> Higher rates of diabetes and hypoparathyroidism among our population were not associated with higher rate of IOC. Earlier studies in thalassemia major showed that IOC was a particular type of cardiomyopathy with complex pathophysiology and not just a direct effect of iron infiltration.<sup>14,15</sup> Immuno-inflammatory and genetic factors seemed to contribute to the pathogenesis of IOC, such as myocarditis, the HLA genotype, and the apolipoprotein E genotype.<sup>15,16</sup> The role of genetic factors and its contribution to the lower IOC rate among our patients need to be studied.

The United Arab Emirates is one of the highest countries in diabetes prevalence worldwide,<sup>17</sup> which may in part explain the high rate of diabetes mellitus among our patients. Diabetes mellitus in thalassemia is peculiar in many aspects including its pathophysiology.<sup>18</sup> It has been attributed to impaired secretion of insulin secondary to chronic pancreatic iron overload and to insulin resistance as a consequence of iron deposition within liver or skeletal muscle.<sup>18-21</sup> Diabetes has been linked to immune system activation against

pancreatic cells through iron deposition with selective oxidative damage to beta cells<sup>22</sup> and has also been linked to episodes of acute viral hepatitis in some patients.<sup>23</sup> Although genetic predisposition was described, there was little data on its contribution to diabetes development in thalassemia major.<sup>8,18</sup> Another point of note is that the high overall rate of hypoparathyroidism (10.5%) observed in our population was also observed in Saudi Arabia, reaching 20%.<sup>24</sup>

Females had statistically significant lower serum ferritin compared to males. Only 2 females had cardiomyopathies compared to 5 males, although 50.5% of the studied population was male. This was consistent with earlier reports that females with thalassemia major treated with transfusion and DFO have better survival and a lower frequency of heart failure and arrhythmia.<sup>9</sup> A better survival in females has also been observed in sickle cell anemia<sup>25</sup> and the same was observed in the majority of the world populations.<sup>26</sup>

The results of this study show that iron overload related complications among our patients with thalassemia major were different from those reported internationally; this information can be of great help in genetic counseling. The high complications prevalence among our population stresses the need for further improvement in the management of these complex patients. Studying the genetic status of thalassemia major patients in our area may uncover the underlying genetic modifiers of iron overload impact on the heart and endocrine organs. This may explain the low cardiomyopathy rate and the high diabetes and hypoparathyroidism rate among our population. Moreover, this data will be of great use when we evaluate the impact of the recently introduced oral iron chelators and technologies such as cardiac MR and FerriScan to quantify organ iron status.

Our study had several limitations. Being retrospective, data source limitation made it difficult to evaluate survival and complication-free survival curves. Data on adherence to treatment were not available for our series of patients. Data on direct measurements of hepatic iron or cardiac MR was not available either.

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