

# Prevalence of Endocrinopathies in Patients with Beta-Thalassaemia Major - A Cross-Sectional Study in Oman

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## Abstract

**Background:** Beta-thalassaemia major is a common medical problem worldwide. There is little data dealing with the nature and prevalence of different endocrine disorders in this disease in the Sultanate of Oman.

**Objectives:** To establish the prevalence and times of occurrence of endocrine disorders in patients with beta-thalassaemia major.

**Methods:** This cross-sectional study was conducted during Jan-Jul 2008 and dealt with 30 Omani patients with transfusion-dependent homozygous beta-thalassaemia major who were consulting Thalassaemia Clinic, Royal Hospital. They included 15 males and 15 females, aged 16 to 32 years with median of 21 years and mean  $\pm$  SD of  $21.23 \pm 3.42$  years. The medical records of these patients were reviewed and their endocrine functions were assessed. This assessment included pituitary and gonadal function, thyroid function, bone profile (including Parathyroid Hormone), morning cortisol and fasting glucose. These profiles were reviewed to exclude hypogonadism, hypothyroidism, hypoparathyroidism, hypoadrenalism or diabetes mellitus.

**Results:** Hypogonadism was reported in 22 (73.3%) patients (13 female, 9 male). Low levels of Follicle-Stimulating Hormone (FSH) and low Luteinizing Hormone (LH) with low estradiol (in females) or testosterone (in males) was noted in 15 (50.0%) patients (7 female, 8 male). Normal (but inappropriately low) levels of FSH and LH with low estradiol (in females) or testosterone (in males) was noted in 7 (23.3%) patients (6 female, 1 male). Primary hypothyroidism was present in only 1 (3.3%)

patient (female) who Hypoparathyroidism was found in 3 (10.0%) patients (2 female, 1 male). Diabetes mellitus with high fasting glucose was noted in 8 (26.7%) patients (2 female, 6 male). Morning cortisol levels for all patients were within the reference range with no suspicion of hypoadrenal cortical function. Eight (26.7%) patients had no endocrine disorder, 12 (40.0%) patients had one disorder, 8 (26.7%) patients had 2 disorders, and 2 (6.7%) patients had 3 endocrine disorders. There was no significant difference ( $p > 0.050$ ) in mean serum ferritin in thalassaemics with or without endocrinopathy, regardless of the number of endocrinopathy.

**Conclusion:** There is high prevalence of endocrine disorders among Omani beta-thalassaemic adult patients. This signifies the importance of awareness for their development and monitoring for early detection and replacement therapy. No relationship between serum ferritin and development of endocrinopathy was noted.

**Keywords:** Beta-thalassaemia; Endocrinopathy.

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## Introduction

Hæmoglobinopathies are common in Oman.<sup>1</sup> Data from a community-based survey of the most common genetic blood disorders among Omani children has reported a prevalence rate of 2% for beta-thalassaemia trait, 0.07% for beta-thalassaemia major, 6% for sickle cell trait and 0.2% for sickle cell disease.<sup>2</sup> Comparable data has also been reported in other GCC and neighboring countries.<sup>3,4,5,6</sup>

Beta-thalassaemia major is an inherited monogenic disorder that was first described by Cooley and Lee.<sup>7</sup> It is caused by a mutation at the  $\beta$ -globin gene locus resulting in persistence of  $\alpha$ -globin chain that is precipitated within erythroid precursors in the bone marrow associated with severe dyserythropoietic anaemia.<sup>8</sup> The combination of early diagnosis, improvement in monitoring complications and advances in supportive therapy has

enabled patients with thalassaemia major to have improved life expectancy.<sup>9</sup> The cornerstone in management is life-long blood transfusion with frequent iron chelation therapy to minimize the deleterious effect of chronic iron deposition and accumulation in tissues.<sup>8</sup> Despite this, these patients are prone to long-term organ dysfunction particularly the cardiovascular, hepato-biliary, endocrine and skeletal systems.<sup>10</sup>

The objective of this study was to establish the spectrum and prevalence rates and times of onset of endocrine disorders in Omani transfusion-dependent beta-thalassaemia adult patients.

## Methods

This cross-sectional study was conducted during the period (1<sup>st</sup> Jan- 31<sup>st</sup> Jul 2008) and dealt with Omani patients with

transfusion-dependent homozygous beta-thalassaemia major who were consulting the adult Thalassaemia Clinic, Royal Hospital, Sultanate of Oman. It included 30 patients (15 male, 15 female), aged 16 to 32 years with median of 21 year and mean  $\pm$  SD of 21.23  $\pm$  3.42 years. Each patient was consulting the clinic at 3 monthly intervals. The diagnosis of homozygous thalassaemia was based on the characteristic haematological criteria (peripheral blood evaluation and haemoglobinopathy screening) at presentation or screening from early years of life.

The study protocol was a naturalistic observation, an integral part of routine clinical procedure through reviewing the medical records of these thalassaemic patients from the hospital computer records including the haematologists' and endocrinologists' clinical review as well as results of laboratory investigations. The clinical haematologists are regularly performing the management of these patients which includes supervision of blood transfusion and chelation therapy, as well as monitoring of organs' dysfunction due to predicted iron deposition in tissues. The patients were regularly transfused with packed red cells every three weeks since early years of life, and were regularly taking iron chelator as Desferrioxamine (40 mg/kg body weight) subcutaneous infusion 5 days per week, and Deferiprone (75 mg/kg body weight) tablet daily.

For the laboratory investigations, blood samples were drawn from all patients in fasting state in the morning during their regular visits. In addition to complete blood count and serum ferritin, biochemical endocrine profiles were done to screen for any possible dysfunction. Evaluation for endocrine complications is usually performed regularly, together with other routine function profiles tests. The investigations include: pituitary-gonadal function test (FSH, LH, prolactin, estradiol in females and testosterone in males), thyroid function test (FT4 and TSH), bone profile (calcium, phosphorus, albumin, alkaline phosphatase and PTH), morning cortisol and glucose. These profiles were performed to exclude any possible hypogonadism, hypothyroidism, hypoparathyroidism, hypoadrenal cortisolism or diabetes mellitus. All the parameters were measured in the Clinical Biochemistry Laboratory, Royal Hospital. Serum FSH, LH, prolactin, estradiol, testosterone, FT4, third generation TSH, intact PTH, cortisol and ferritin were measured by chemiluminescent microparticle immunoassay methods on Architect 2000 System (Abbott, USA). Serum calcium was measured by ion selective electrode, inorganic phosphorus by molybdenum blue, albumin by bromocresol purple, alkaline phosphatase by kinetic rate method, and glucose by timed end point hexokinase method, all on Synchron LX20 (Beckman, USA)<sup>11</sup>.

Laboratory evidence for hypogonadism was based on finding low FSH and LH with low estradiol or testosterone (hypogonadotrophic hypogonadism), or normal (but inappropriately low) FSH and LH with low estradiol or testosterone (normogonadotrophic hypogonadism). Hypothyroidism was defined based on high TSH (primary) or low TSH (secondary) with low FT4. Hypoparathyroidism was diagnosed based on low corrected calcium concentration, high phosphorus and inappropriately low PTH. Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association (1997). Hypoadrenalism (hypocortisolism) was based on finding low morning cortisol level.<sup>11</sup>

The results were analyzed and numerical data presented as mean  $\pm$  SD with median and range. The prevalence rate of endocrinopathy was calculated as single or multiple endocrine organ involvement. The statistical difference in serum ferritin between the different groups of patients with or without endocrinopathies was assessed using unpaired student's test.<sup>12</sup> The statistical significance was assigned for  $p < 0.050$ .

## Results

The prevalence rates of endocrinopathies/endocrine disorders are shown in Table 1. Hypogonadism was reported in 22 (73.3%) patients (13 female, 9 male). Low FSH  $\leq 1.5$  U/L (median, range; 0.6, 0.1-1.5 U/L) and low LH  $\leq 1.5$  U/L (0.3, 0.1-1.1 U/L) with low estradiol  $< 100$  nmol/L (6 patients  $< 37$  nmol/L, 1 patient 88 nmol/L) in females, and low testosterone  $< 9.0$  nmol/L (0.9, 0.3-2.2 nmol/L) in males, indicative of hypogonadotrophic hypogonadism was noted in 15 (50.0%) patients (7 female, 8 male). On the other hand, normal (but inappropriately low) level of FSH (3.6, 2.6-7.4 U/L) and LH (2.6, 2.3-15.0 U/L) with low estradiol (43, 37-88 nmol/L) in females and low testosterone (6.9 nmol/L in the only one male) indicative of normogonadotrophic hypogonadism was noted in 7 (23.3%) patients (6 female, 1 male).

Primary hypothyroidism was present in only 1 (3.3%) female patient who had high TSH and low FT4. There was no evidence of secondary hypothyroidism. Hypoparathyroidism was found in 3 (10.0%) patients (2 female, 1 male) who were presented with low corrected calcium of  $< 2.1$  mmol/L (median, range; 1.42, 1.34-1.45 mmol/L), high inorganic phosphorus of  $> 1.4$  mmol/L (2.87, 2.47-3.3 mmol/L) and inappropriately low PTH (1.3, 1.3-1.7  $\mu$ g/L). Diabetes mellitus with fasting glucose  $\geq 7.0$  mmol/L (12.5, 8.0-24.2 mmol/L) was noted in 8 (26.7%) patients (2 female, 6 male). Six patients (1 female, 5 male) had severe hyperglycaemia and

were treated by insulin, and two patients (both males) had records of presentation with ketoacidosis. Morning cortisol levels for all patients were within the reference range (250-550 nmol/L) and no patient showed suspicion of hypocortisolism or hypoadrenal cortical function.

Table 2 shows the prevalence of endocrinopathy according to the number of endocrine disorders (hypogonadism, hypothyroidism, hypoparathyroidism or diabetes mellitus). Certain patients had more than one endocrine disorder. Accordingly, 8 (26.7%) patients had no endocrine disorder, 12 (40.0%) had one disorder, 8 (26.7%) had 2 disorders, and 2 (6.7%) had 3 endocrine disorders. There was no significant difference ( $p > 0.050$ ) in mean serum ferritin in

thalassaemic patients with or without endocrinopathy (Table 1), regardless of the number of endocrine glands involved (Table 2).

In concern with therapy, thalassaemics with hypogonadism were on oestrogen-progesterone combination therapy as oral contraceptive pills with Progylton tablets (in females), and monthly testosterone injection (in males). The single thalassaemic patient with hypothyroidism was placed on L-thyroxine therapy. Thalassaemics with hypoparathyroidism were on daily maintenance dose of vitamin D, alfa.1.calcidol and calcium carbonate supplement. Of the 8 diabetics, 6 were treated by insulin and 2 were on oral hypoglycaemic drugs.

**Table 1:** Prevalence of endocrinopathies in 30 homozygous beta-thalassaemic patients\*

Parameter	Hypogonadism		Hypoparathyroidism	Hypo Thyroidism	Diabetes Mellitus	No Endocrinopathy	
	Hypo Gonadotrophic	Normo Gonadotrophic					
No. (M/F)	15 (8/7)	7 (1/6)	3 (1/2)	1 (0/1)**	8 (6/2)	8 (6/2)	
Prevalence	50%	23.3%	10.0%	3.3%	26.7%	26.7%	
Age at Diagnosis (years)	Mean ± SD	17.5±4.96	18.57±2.76	17.0±3.6	15	17.6±2.1	-
	Median	16.0	19.0	16	-	17.5	-
	Range	13-32	15-22	14-21	-	15-21	-
Age at Study (years)	Mean ± SD	21.0±3.48	21.57±3.82	22.3±4.1	16	21.5±2.39	20.0±2.6
	Median	21.0	23.0	19.0	-	21.0	20.0
	Range	18-32	17-28	19-27	-	19-27	17-24
Ferritin (µg/L)	Mean ± SD	5794±3413	7726±2620	5348±2038	4950	6445±3979	5647±3663
	Median	6030	7424	5744	-	6257	5014
	Range	568-4318	4318-12473	3933-7951	-	1576-12540	865-11809
Significance of difference in Ferritin (P)***	0.838	0.191	0.812	-	0.618	-	

\* : no patient had hypocortisolism

\*\* : only one patient had hypothyroidism, statistical data are not presented

\*\*\* : significance of difference in ferritin in comparison with patients without endocrinopathy

**Table 2:** Prevalence of endocrinopathies according to the number of disorders in 30 homozygous beta-thalassaemic patients\*

Parameter	Number of Endocrinopathy			
	0	1	2	3
No. (M/F)	8 (6/2)	12 (3/9)	8 (4/4)	2 (1/1)**
Prevalence	26.7%	40%	26.7%	6.7%
Age at Study (years)	Mean $\pm$ SD	20.0 $\pm$ 2.6	21.6 $\pm$ 3.0	21.4 $\pm$ 4.4
	Median	20.0	22.0	20.5
	Range	17-24	17-28	18-32
Ferritin ( $\mu$ g/L)	Mean $\pm$ SD	5647 $\pm$ 3663	6825 $\pm$ 2661	6425 $\pm$ 3638
	Median	5014	7166	6257
	Range	865-11809	3248-12473	568-12540
Significance of difference in Ferritin (P)***	-	0.390	0.609	-

\* : endocrinopathies included: hypogonadism, hypoparathyroidism, hypothyroidism, diabetes mellitus

\*\* : only two patients had 3 endocrinopathies, data of significance in ferritin is not applicable

\*\*\* : significance of difference in ferritin in comparison with patients without endocrinopathy

## Discussion

Patients with beta-thalassaemia major are prone to metabolic complications, including endocrine dysfunction which can occur as single or multiple endocrine glands' involvement. Although the actual mechanism is not definitive, however, the most likely explanation is related to iron overload and its burden, in addition to lipid peroxidation, oxidative stress and free radicles release.<sup>13</sup>

In the current report, high prevalence of endocrine abnormalities was observed in beta-thalassaemic patients, which is in agreement with the reports by several authors.<sup>14, 15, 16</sup> Hypogonadism was the most frequent endocrine disorder, with 73.3% patients being affected (50% hypogonadotrophic and 23.3% normogonadotrophic). In term of sex, out of 15 females, 13 were affected, and out of 15 males, 9 were affected. All of our patients are in the second or third decade of life (median 21 years, range 16-32 years), which had raised the risk of involvement. It has been reported that the pituitary-gonadal axis is very sensitive to iron deposition leading to hypofunction of these glands, particularly in the form of secondary hypogonadism, which is rarely reversible even with iron chelation therapy.<sup>17</sup> In comparison with others, hypogonadism has been reported from 17% to 69%, and in another study up to 62% in boys and 75% in girls with beta-thalassaemia major.<sup>14, 18, 19</sup> Hormone replacement therapy is recommended, however the age of initiation and dosage should be balanced with coexistence of other organs' dysfunction particularly heart, liver and skeletal systems.<sup>20</sup> In our patients, the affected females were on oestrogen-progesteron combination therapy as oral contraceptive

pills with Proglyton tablets, and affected males were on monthly testosterone injection, as replacement therapy. Other possible causes of hypogonadism include associated liver disorder, chronic hypoxia, diabetes mellitus, free radicle oxidative stresses, and zinc deficiency.<sup>21</sup>

Primary hypothyroidism was observed in only one patient (3.3%) of our thalassaemics, who was placed on L-thyroxine replacement therapy following diagnosis. It seems that hypothyroidism is a rare complication in Omani thalassaemics and its prevalence was lower than that reported by others. This is comparable to another cohort study which reported low prevalence of hypothyroidism of 4.0% in beta-thalassaemia, although 26.9% of their patients with normal thyroid function showed an exaggerated TSH response to TRH test.<sup>22</sup> However, in a recent survey, a high prevalence of primary overt hypothyroidism was present in 16% of beta-thalassaemic patients.<sup>23</sup> The disorder is mostly due to iron deposition in the thyroids. However, the thyroid pituitary axis seems to be less sensitive to iron deposition damage than gonadal and GH axis. Hence, secondary hypothyroidism is rare in thalassaemic patients, which was not observed in our series, as also in other reports.<sup>22, 24</sup> In studies with low prevalence of overt hypothyroidism, mild thyroid dysfunctions were more common as reported in 12.5% of patients.<sup>22</sup> In our series, mild thyroid dysfunction (subclinical hypothyroidism) was also reported only in one patient (3.3%).

Disturbance of calcium homeostasis is also known in thalassaemia major that could be due to hypoparathyroidism, vitamin D deficiency, bone marrow expansion or chronic liver involvement. Three thalassaemic patients (10.0%) in our series

had evidence of primary hypoparathyroidism, of whom 2 had two additional endocrinopathy and 1 had another endocrinopathy. In comparison with others, a prevalence of hypoparathyroidism from 3.6% to 13.5% had been reported.<sup>15, 25</sup> In a similar study in Saudi Arabi, Aleem *et al* reported hypoparathyroidism in 20% of the 40 thalassaemic patients reviewed.<sup>26</sup> Also, high prevalence for hypocalcaemia of 41% has been observed by Najafipour *et al*.<sup>23</sup> Although, hypoparathyroidism was reported to be more common in males with male/female ratio of 4:1,<sup>15</sup> however in our series it was observed more in females with a ratio of 1:2. Periodic assessment of bone profile in addition to vitamin D status is recommended and maintenance of normal serum calcium is important to avoid the risk of arrhythmias particularly in the presence of cardiomyopathy. Our thalassaemic patients who had hypoparathyroidism were on daily maintenance dose of vitamin D, alfa.1.calcidol and calcium carbonate supplement. Osteopenia is more common in thalassaemics with its prevalence reported to be 45-51%.<sup>25, 27</sup>

Diabetes mellitus was observed in 8 (26.7%) patients, of whom 6 patients (5 male, 1 female) had severe hyperglycaemia and were treated by insulin. Among the mechanisms involved for precipitating diabetes mellitus, iron overload in the pancreatic beta-cells leading to pancreatic dysfunction is the most likely one.<sup>28</sup> Other contributing factors include insulin resistance, liver dysfunction, genetic predisposition or family history of diabetes.<sup>29</sup> Studies had reported prevalence of diabetes mellitus in beta-thalassaemic patients to range up to 24%.<sup>30</sup> Diabetes appears to be unusual in beta-thalassaemics of less than 16 years old.<sup>31</sup> In our thalassaemics, a state of hypocortisolism was not noted and there was no clinical suspicion for the involvement of ACTH or adrenal gland. Reports have indicated that iron deposition may occur in the adrenals particularly in the zona glomeruloza and only when this is severe, it will interfere with its function.<sup>32</sup>

Finally, in the thalassaemic patients reviewed, no relationship between serum ferritin level and development of endocrinopathy was observed. There was no significant difference in mean ferritin in thalassaemic patients with or without endocrinopathy, as well as in patients without or with one or more endocrinopathy. There is contradiction between the different studies, with some revealing a positive relationship,<sup>14, 28, 30, 31</sup> while others did not.<sup>22, 24, 27</sup> Although high ferritin level is an indicator of iron overload, however being a positive acute phase protein, it is increased in the presence of associated acute and chronic disorders particularly inflammatory and hepatic conditions, such as chronic hepatitis.<sup>33</sup> This may affect and limit the validity and effectiveness of ferritin in reflecting iron status in beta-thalassaemia.

## Conclusion

There is high prevalence of certain endocrine disorders among Omani adult homozygous beta-thalassaemic patients. This signifies the importance of therapeutic intervention and medical awareness for their development which necessitates the importance of frequent follow-up and monitoring for early detection and replacement therapy. No relationship between serum ferritin level and development of endocrinopathy was noted.

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