Original Article

Severe Liver Iron Concentrations (LIC) in 24 Patients with β-Thalassemia Major: Correlations with Serum Ferritin, Liver Enzymes and Endocrine Complications

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Abstract. *Introduction:* **Chronic blood transfusion is the mainstay of care for individuals with β-thalassemia major (BTM). However, it causes iron-overload that requires monitoring and management by long-term iron chelation therapy to prevent endocrinopathies and cardiomyopathies, which can be fatal. Hepatic R2 MRI method (FerriScan®) has been validated as the gold standard for evaluation and monitoring liver iron concentration (LIC) that reflects the total body iron-overload. Although adequate oral iron chelation therapy (OIC) is promising for the treatment of transfusional iron-overload, some patients are less compliant with it, and others suffer from long-term effects of iron overload.**
Objective: **The aim of our study was to evaluate the prevalence of endocrinopathies and liver dysfunction, in relation to LIC and serum ferritin level, in a selected group of adolescents and young adult BTM patients with severe hepatic iron overload (LIC from 15 to 43 mg Fe/g dry weight).**
Patients and Methods: **Twenty-four selected BTM patients with severe LIC, due to transfusion-related iron-overload, followed at the Haematology Section, National Centre for Cancer Care and Research, Hamad Medical Corporation of Doha (Qatar), from April 2015 to July 2017, were retrospectively evaluated. The prevalence of short stature, hypogonadism, hypothyroidism, hypoparathyroidism, impaired fasting glucose (IFG), diabetes, and adrenal insufficiency was defined and assessed according to the International Network of Clinicians for Endocrinopathies in Thalassemia (ICET) and American Diabetes Association criteria.**
Results: **Patients' most common transfusion frequency was every three weeks (70.8%). At the time of LIC measurements, their median age was 21.5 years with a mean age of 21.7± 8.0 years. Mean LIC was 32.05 ± 10.53 mg Fe/g dry weight (range: 15 to 43 mg Fe/g dry weight), and mean serum ferritin level was 4,488.6 ± 2,779 μg/L. LIC was correlated significantly with serum ferritin levels (r = 0.512; p = 0.011). The overall prevalence of short stature was 26.1% (6/23), IFG was 16.7% (4/24), sub-clinical hypothyroidism was 14.3% (3/21), hypogonadotropic hypogonadism was 14.3% (2/14), diabetes mellitus was 12.5% (3/24), and biochemical adrenal insufficiency was 6.7% (1/15). The prevalence of hepatitis C positivity was 20.8% (5/24). No case of clinical hypothyroidism, adrenal insufficiency or hypoparathyroidism was detected in this cohort of patients. The prevalence of IFG impaired fasting glucose was significantly higher in BTM patients with very high LIC (>30 mg Fe/g dry liver) versus those with lower LIC (p = 0.044). The prevalence of endocrinopathies was not significantly different between the two**

groups of patients with LIC above and below 15 mg Fe/g dry weight.
Conclusions: **A significant number of BTM patients, with high LIC and endocrine disorders, still exist despite the recent developments of new oral iron chelating agents. Therefore, physicians' strategies shall optimize early identification of those patients to optimise their chelation therapy and to avoid iron-induced organ damage. We believe that further studies are needed to evaluate if serial measurements of quantitative LIC may predict the risk for endocrine complications. Until these data are available, we recommend a close monitoring of endocrine and other complications, according to the international guidelines.**

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Introduction. Chronic blood transfusion (CBT) is the mainstay of care for individuals with β-thalassemia major (BTM) for preventing growth retardation, skeletal changes that result from the expansion of the bone marrow, and development of masses from extramedullary hematopoiesis.[1] In spite of that, CBT causes iron-overload that requires monitoring and management through long-term iron chelation therapy. With inadequate chelation therapy, cardiac arrhythmias, cardiomyopathy, and heart failure are the predominant causes of death, while endocrine abnormalities and chronic liver disease contribute significantly to morbidity and mortality.[1]

In general, iron chelation therapy should be started as soon as the patient becomes significantly iron loaded. Significant iron load correlates with serum ferritin of approximately 1,000 ng/mL. Liver iron concentration (LIC) is considered the best measure of total iron loading. LIC should be at least 3 mg Fe/g dry weight before starting chelation.[1]

Overall, iron chelation therapy results in better overall survival, especially if it is instituted early and compliance is maintained. In particular, the second-generation of oral agents appears to be associated with improved overall and event-free survival in transfusion-dependent patients with β-thalassemia.[2]

Very little is known about the relationship between mild/moderate iron overload assessed by LIC and endocrinopathies in patients with BTM,[3]

and nothing has been reported in the literature, to the best of our knowledge, about the prevalence of disease-specific endocrinopathies in patients with severe iron overload.

The present study aims to report the prevalence of endocrinopathies and liver dysfunction, in relation LIC and serum ferritin level, in a selected group of adolescents and young adults with BTM and severe iron overload, assessed by hepatic R2 MRI method (FerriScan®).

Patients and Methods. This retrospective cohort study was performed on 24 adolescents and young adults with BTM and severe LIC (from 15 to 43 mg Fe/g dry weight), secondary to transfusion-related iron-overload, followed at the National Centre for Cancer Care and Research (NCCCR), Doha (Qatar) over 27 months (from April 2015 to July 2017).

The prevalence of endocrinopathies in 28 TM patients followed at the NCCCR with a LIC strictly under 15 mg Fe/g dry weight was also registered to assess the differences between the two groups of patients.

The patients' medical history (including blood transfusion regime and chelation therapy), the growth percentiles and pubertal stages (standing height, weight, body mass index - BMI - and Tanner's stages) were also reviewed.

Laboratory investigations included measurement of their serum ferritin (SF), alkaline phosphatase (ALP), lactate dehydrogenase (LDH),

total bilirubin, alanine transferase (ALT), aspartate transferase (AST), fasting blood glucose (FBG), hemoglobin A1C (HbA1c), morning cortisol level (Cort-AM), insulin-like growth factor (IGF-1), parathyroid hormone (PTH), corrected calcium (Ca Corr), phosphate (PO4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (in males), estradiol (in females), thyroid stimulating hormone (TSH), and free thyroxine (FT4).

SF and hormonal parameters were measured by immune-enzymatic and electrochemiluminescence immunoassays. The manufacturer's normal reference range values for SF were 30–350 ngm/L, in males, and 15–150 ng/mL in females.

Iron status was classified as mild (serum ferritin <1,000 ng/mL), moderate (serum ferritin >1,000 ng/ml and <2,000 ng/mL) or severe (serum ferritin >2,000 ng/mL).

Liver iron content (LIC) was measured by FerriScan ® and values were expressed in mg Fe/g weight.[4] Four classes of LIC have been reported in thalassemic patients: Class 1=normal LIC < 3 mg Fe/g dry liver, Class 2=mild overload LIC 3–7 mg Fe/g dry liver, Class 3=moderate LIC overload 7–15 mg Fe/g dry liver, and Class 4=severe LIC overload ≥15 mg Fe/g dry liver.[5]

Short stature and endocrine complications were assessed and defined according to the International Network of Clinicians for Endocrinopathies in Thalassemia (ICET) and American Diabetes Association criteria.[6,7]

Ethical approval for the study was obtained by the IRB of Medical Research Center at Hamad Medical Corporation [http://www.wma.net]. All procedures were carried out with the adequate understanding and consent of patients.

The Kolmogorov-Smirnov (K-S) test and PP plot were used to test for normality of the data. Associations between two or more qualitative variables were assessed using chi-square (χ^2), Fisher Exact or Yates corrected Chi-square statistical tests as appropriate. Quantitative data between the two independent groups were analysed using unpaired 't' test or Mann Whitney U test as appropriate. The relationship between two quantitative variables was examined using Pearson's correlation coefficients. Pictorial presentations of the key were made using appropriate statistical graphs. All p values presented were two-tailed, and p values <0.05 was considered as statistically significant. All Statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL) and Epi-info (Centres for Disease Control and Prevention, Atlanta, GA) software.

Results. Out of the twenty-four transfusion-dependent BTM, 63% (15/24) were males and 37% (9/24) were females. There were eight different nationalities, but Pakistanis accounted for almost one-third (29.2%) and Qataris for one-fifth (20.8%), whereas Egyptians, Sudanese, Bangladeshis, Iranians, Palestinians and Bahrainis accounted for 12.5%, 12.5%, 8.3%, 8.3%, 4.2% and 4.2%, respectively.

BTM patients had been regularly transfused over the past 19.7±8.0 years (range: 7-33 years), starting from the age of 2 years. Transfusion frequencies were as follows: every three weeks accounted for 70.8% (17/24 patients), every four weeks 16.7% (4/24) and every two weeks 12.5% (3/24).

21 out of 24 BTM patients referred a "regular" chelation therapy; 18/24 were using deferasirox, 1/24 was using deferoxamine, and 2/24 were using combined deferasirox and deferoxamine therapy. Moreover, 3 out of 24 patients referred a poor chelation therapy (**Table 1**).

Before LIC assessment by FerriScan®, patients using deferasirox, deferoxamine or both (**Table 1**) had been on iron chelation therapy, starting from the age of 4 years, for the past 15.3±5.4 years. Their mean age at the time of LIC measurements was 21.7±8.0 years (range: 9-35 years).

Patients' mean standing height was 158.2±11.4 cm, mean weight was 54.1±13.9 kg, and mean BMI was 21.5±5 Kg/m². The mean LIC at the

Table 1. Iron chelation therapy.

Chelating agent		Exposure to treatment (mean: mg/kg/day)
Deferasirox	75% (18/24)	29
Deferoxamine	4.2% (1/24)	55
Deferasirox + Deferoxamine	8.3% (2/24)	29 Deferasirox + 37 Deferoxamine
Poor chelation therapy with Deferasirox	12.5% (3/24)	29

time of the study was 32.05±10.53 mg Fe/g dry weight (range:15- 43 mg Fe/g dry weight; 43 mg Fe/g dry weight being the upper limit for FerriScan® values). Mean SF at LIC measurements was 4,488±2,779 ng/mL (range: 453-11,117 ng/mL). Biochemical (AST, ALT, ALP, LDH and total bilirubin) and hormonal data are shown in **table 2**.

LIC was correlated significantly with morning cortisol levels (r = 0.539, p = 0.038), but not with any of the hormonal levels. There was also a significant correlation between LIC and SF in BTM patients (r = 0.512, p = 0.011).

SF was correlated significantly with TSH (r = 0.603, p = 0.004) and IGF-1 (r = -0.611, p = 0.012) concentrations (**Table 3** and **Figure 1**).

The overall prevalence of endocrinopathies was as follows = short stature: 26.1% (6/23), IFG: 16.7% (4/24), sub-clinical hypothyroidism: 14.3% (3/21), hypogonadotropic hypogonadism: 14.3% (2/14), diabetes insulin dependent: 12.5% (3/24), and biochemical hypocortisolism: 6.7% (1/15). A single endocrinopathy was present in 7 patients out of 24 (29.2%) and 2 or more endocrinopathies

Table 2. Patients' characteristics, biochemical and hormonal parameters.

	Number of patients	Normal range	Mean ± SD	Min	Max
Generalities					
Age* (years)	24/24		21.75 ± 8.05	9	35
Height* (cm)	23/24		158.2 ± 11.4	127	170
Weight* (kg)	23/24		54.1 ± 13.9	24	84
BMI* (kg/m²)	23/24	18-25	21.5 ± 5.1	14.9	38.3
Splenectomy*	1/24				
LIC (mg Fe/g dry weight)	24/24	1.0-3.0	32.05 ± 10.53	15	> 43
SF* (ng/mL)	24/24	Male: 30-350 Female: 15-150	4,488 ± 2,779	453	11,117
Liver enzymes					
AST* (U/L)	24/24	0-37	52.0 ± 34.1	15	150
ALT* (U/L)	24/24	0-40	61.9 ± 50.3	13	197
ALP* (U/L)	24/24	40-130	145.0 ± 109.5	63	536
LDH* (U/L)	9/24	141-231	284.8 ± 115.5	149	423
Total bilirubin* (µmol/L)	24/24	0-21	45.3 ± 32.1	4.5	147
Endocrine values					
TSH* (mIU/L)	21/24	0.45-4.5	2.8 ± 1.9	0.9	8.8
FT4* (pmol/L)	21/24	9.0-20	12.5 ± 1.4	10.4	16.5
LH* (IU/L)	19/24	*Female:* Follicular phase= 2-11 *Male*: 1-9	3.8 ± 2.4	0.8	8.8
FSH* (IU/L)	19/24	*Female*: Follicular phase= 4-9, *Male*: 1-19	4.0 ± 3.3	1	12.5
Testosterone* (nmol/L - Male)	8/15	10.0-35	28.3 ± 16.0	7.8	56.7
Estradiol* (pmol/L - Female)	3/9	Follicular phase: 88-420, Midcycle: 230-2000, Luteal phase: 300-1100	239.3 ± 258.8	82	538
PTH* (pg/mL)	21/24	15-65	40.0 ± 25.5	9	87
Ca Corr* (mmol/L)	24/24	2.1-2.6	2.3 ± 0.1	2	2.5
Ph* (mmol/L)	15/24	0.87-1.45	1.4 ± 0.3	0.9	2
IGF-1* (µg/L)	16/24	115-500	141.7 ± 72.6	48	288
Cortisol-AM* (nmol/L)	15/24	138-580	290.7 ± 117.9	108	513
Fasting Glu* (mmol/L)	24/24	4.0-6.0	6.4 ± 3.6	4.1	21.6
HbA1c* (%)	7/24	4.0-5.6	7.2 ± 1.7	4.5	8.5

Legend: (*****) at LIC measurements; Liver iron concentration (**LIC**); body mass index (**BMI**); serum ferritin (**SF**); alkaline phosphatase (**ALP**); lactate dehydrogenase (**LDH**), alanine transferase (**ALT**); aspartate transferase (**AST**); fasting glycaemia (**Fasting Glu**); morning cortisol level (**Cort-AM**), insulin-like growth factor (**IGF-1**); parathyroid hormone (**PTH**); corrected calcium (**Ca Corr**), phosphate (**Ph**); luteinizing hormone (**LH**); follicle-stimulating hormone (**FSH**); thyroid stimulating hormone (**TSH**); free thyroxine (**FT4**).

Table 3. Correlations of LIC with serum ferritin, endocrine parameters and liver enzymes.

		LIC mg/g/dw	Serum ferritin
Serum ferritin (ng/mL)	Pearson Correlation	.512	
	Sig. (2-tailed)	.011	
TSH (mIU/L)	Pearson Correlation		.603
	Sig. (2-tailed)		.004
IGF-1 (μg/L)	Pearson Correlation		-.611
	Sig. (2-tailed)		.012
Cort-AM (nmol/L)	Pearson Correlation	.539	
	Sig. (2-tailed)	.038	

Figure 1. Correlations of LIC with serum ferritin and cortisol.
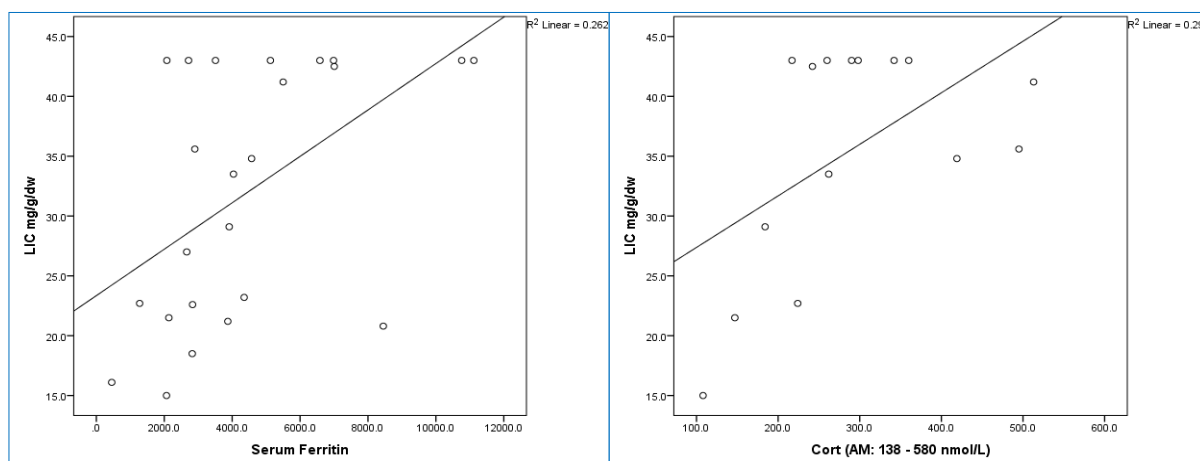
in five patients (20.8%). Five out of 24 patients (20.8%) of patients were hepatitis C antibody positive.

The prevalence of IFG was significantly higher in BTM patients with LIC > 30 vs those with < 30 mg Fe/g dry weight [30.8% (4/13) vs 0 % (0/11), p = 0.044]. On the contrary, the prevalence of short stature and sub-clinical hypothyroidism were non-significantly higher in the group of BTM patients with LIC > 30 vs those with < 30 mg Fe/g dry weight [33.3% (4/12) vs 18.2% (2/11), p = 0.408 and 16.7% (2/12) vs 11.1% (1/9), p = 0.719, respectively] as well as the prevalence of hypogonadism, diabetes and hepatitis C among the two groups of patients.

We also compared these data with those of 28 BTM patients followed at NCCCR with a LIC <15 mg Fe/g dry weight (median age: 19 years, mean age: 21.7 years, range: 8 − 35 years). No statistical differences were observed between the two groups of patients (**Table 4**).

Discussion. BTM is an important cause of morbidity and mortality worldwide. Complications related to chronic transfusion therapy are numerous, affect almost every organ in the body, and vary considerably among patients over the time.[1,2,6] Endocrine organ dysfunction and failures

Table 4. Prevalence of endocrinopathies in BMT patients with LIC ≥ 15 and LIC < 15 mg/g/dw.

Short stature and endocrine complications	LIC ≥ 15 mg/g/dw (n=24)	LIC < 15 mg/g/dw (n=28)	P Value
Short Stature	26.1% (6/23)	7.1% (2/28)	0.083
Impaired Fasting Glucose	16.7% (4/24)	17.9% (5/28)	0.999
Sub-clinical Hypothyroidism	14.3% (3/21)	11.1% (3/27)	0.758
Hypogonadotropic hypogonadism	14.3% (2/14)	9.5% (2/21)	0.695
Diabetes insulin dependent	12.5% (3/24)	10.7% (3/28)	0.85
Biochemical Hypocortisolism	6.7% (1/15)	0% (0/10)	0.601
Hypoparathyroidism	0% (0/21)	12% (3/25)	0.152
Single endocrinopathy	29.2% (7/24)	35.7% (10/28)	0.633
≥ 2 Endocrinopathies	20.8% (5/24)	14.3% (4/28)	0.795

are among the important complications of excessive iron overload.

Sixty-eight patients with BTM and 14 with thalassemia intermedia are regularly followed at the Haematology Section, National Centre for Cancer Care and Research, Hamad Medical Corporation of Doha (Qatar). 24 out of 68 (35.2%) patients with BTM and elevated levels of iron storage, assessed by hepatic R2 MRI method (FerriScan®), were selected for our study because very few data comparing the prevalence of endocrinopathies in relation to the degree of iron overload in adolescents and young adults with BTM are available in the literature.[8,9]

The liver is the main iron storage organ in the body, containing approximately 70% of the total content of the body. Liver iron can be assessed by needle biopsy or, more recently, by non-invasive magnetic resonance imaging (MRI). As liver iron correlates with total body iron, an alternative to evaluating body iron overload is the measurement of LIC.

Measurements of LIC above 1.6 mg Fe/g of dry weight are considered high; there is a small risk of complications when under 7 mg Fe/g dry weight, between 7 and 15 mg Fe/g dry weight are intermediate values and patients with above 15 mg Fe/g dry weight have a risk of serious injury, including fibrosis and cirrhosis of the liver, and cardiac failure.[8]

The lowest LIC level in our patients was 15 mg Fe/g dry weight and the highest 43 mg Fe/g dry weight (the upper limit for FerriScan® assessment), with a mean of 32±10.5 mg Fe/g dry weight.

Despite the relatively young patients' age (mean: 21.7 years; range 9-35 years) and duration of oral iron chelation (OIC; mean:15.3 years), our subjects had a high prevalence of short stature, IFG, hypogonadism, diabetes and subclinical hypothyroidism.

A cross-sectional analytic study, carried out in 2016 on 43 older BTM patients, aged 45-60 years, showed that 88.4% of them suffered from at least one endocrine complication. The majority of patients developed endocrine complications in the second decade of life when serum ferritin level was very high (above 5,000 ng/mL). The very high peak level of serum ferritin registered in these patients was probably due to inadequate doses of deferoxamine in the first years of life, combined with poor compliance to treatment during the peri-pubertal or pubertal age, and to the increased amount of transfused blood not balanced by an increased iron chelating treatment.[9]

Another study done in 2006 from 31 centres in the USA, Canada and the UK found that 56% of BTM patients (age: 25.8±8.1 years) had more than one endocrinopathy with LIC = 19.4±11.4 mg Fe/g dry weight. Endocrinopathies in their patients included diabetes (13%), hypogonadism (40%) and hypothyroidism (10%).[10]

Comparing these data with our study, a lower incidence of hypogonadism was documented, despite the higher LIC levels. There are several potential reasons why BTM patients may not demonstrate the same degree of endocrine organ injury. It is possible that a critical level with prolonged exposure may be necessary to achieve target organ injury.[11] Alternatively, the duration of OIC in our younger patients with BTM (mean age: 21.7±8.0 years), could have partially protected their hypothalamic-pituitary-gonadal axis from the deleterious effects of chronic iron overload.

Furthermore, when compared the prevalence of endocrinopathies with a cohort of 28 BTM patients with a LIC <15 mg Fe/g dry weight (with a relatively same age), the difference between the two groups was not statistically significant. These findings furtherly support the hypothesis that a prolonged iron overload exposure is required in order to induce a detrimental target organ failure.

A low rate of new endocrine disorders and a stabilization of those pre-exisisting were observed in a clinical practice setting by Casale et al. in 86 patients with BTM (mean age: 23.0±12.6 years, range: 5–49).[12]

However, due to the multifactorial causes of endocrine disorders in BTM patients, other factors such as: duration and adherence to prescribed chelation regimens, transfusional iron burden and biological responsiveness to a given chelation regimen could play an additional role in determining the degree of iron overload and development of organs damage.[13-16]

In the Casale et al. study, the median duration of exposure to deferasirox was 6.5 years (range: 3–10) and the mean dose was 25.2±5.1 mg/kg/day (range: 16–36). Improvements were noted in all iron overload indices. LIC values decreased from 5.3 mg Fe/g dry weight (1.0–28.0) to 4.5 mg Fe/g dry weight (p: 0.020). A reduction in serum ferritin level was also noted, from a median of 1,261.0 ng/mL (range 202–7,661) to 1,017 ng/mL

(137–7,234), although the change was not statistically significant (p: 0.165). Overall, 19 (22%) patients interrupted therapy temporarily and 3 (3%) definitively due to alopecia, hemorrhagic gastritis, and skin rash. Reasons for temporary interruptions to treatment included pregnancy in six patients and poor compliance for a 12-month period of the study in one patient.

In our BTM patients, LIC was correlated significantly with morning cortisol levels (r = 0.539, p = 0.038), but not with any of the hormonal levels. SF was correlated significantly with TSH (r = 0.603, p = 0.004) and IGF-1 (r = -0.611, p = 0.012) concentrations.

Is it possible that a single quantitative measurement of LIC is not predictive of endocrinopathy, as suggested by Vichinsky et al.,[17] and multiple serum ferritin measurements over time could be more valuable in predicting complications of iron overload than a single liver biopsy as reported by Telfer et al.[8] Supporting the predictive value of serum ferritin, Gamberini et al.[18] reported that levels of approximately 2,000 ng/mL were found to correlate with hypogonadism, and 3,000 ng/mL for hypothyroidism, hypoparathyroidism and diabetes mellitus, and Shalitin et al.[19] found that an average serum ferritin above 2,500 ng/mL, during puberty, was predictive of hypogonadism and above 3,000 ng/mL, during the first decade of life, was predictive of final short stature.

Therefore, though serum ferritin can be much less accurate in patients with hepatitis C and is weakly correlated with degree of cardiac siderosis,[20] its monthly measurement could still have some value in predicting endocrine complications.

Potential limitations of the study include (a) a single centre with (b) a relatively small sample population, and (c) a detailed knowledge of patients' compliance to chelation therapy. On the other hand, a potential benefit of this single-centre study is the uniformity of the clinical approach and the personal knowledge of patients by doctors and nurses. This is an advantage in particular compared to larger national or international multicentre datasets in which the approaches to patient care across centers and countries maybe variable over the time.

Conclusions. In our study of BTM patients with severe iron overload, short stature was the most common complication followed by IFG, sub-clinical hypothyroidism, hypogonadism, and diabetes mellitus. The prevalence of IFG was significantly higher in BTM patients with LIC >30 mg Fe/g dry weight versus those with lower LIC. Whereas the prevalence of endocrinopathies was not significantly different between the two groups of patients with LIC above and below 15 mg Fe/g dry weight. SF was correlated significantly with TSH and IGF-1 levels, and LIC correlated significantly with SF levels.

Guidelines for the management of TM patients recommend, based mostly on expert opinion, that LIC assessment should be done at 1–2 year intervals (or more frequently depending on iron overload status).[21-23] We believe that further studies are needed to evaluate if serial measurements of quantitative LIC may predict the risk for endocrine glands damage. Until these data are available, we recommend a close monitoring of endocrine and other complications, according to the international guidelines, although some aspects of BTM management remain controversial with clear absence of strong evidence-based recommendations.

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