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ORIGINAL ARTICLE

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Evaluation of endocrine complications in beta-thalassemia intermedia (β-TI): a cross-sectional multicenter study

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Abstract

Background Data on the prevalence and type of endocrine disorders in β-thalassemia intermedia (β-TI) patients are scarce. This multicenter study was designed to determine the prevalence of endocrine complications and the associated risk factors in a large group of β-TI patients.

Methods In this cross-sectional multicenter study, 726 β-TI patients, aged 2.5–80 years, registered at 12 thalassemic centers, from nine countries, were enrolled during 2017. In a subgroup of 522 patients (mean age 30.8 ± 12.1; range: 2.5–80 years) from Qatar, Iran, Oman, Cyprus, and Jordan detailed data were available.

Results Overall, the most prevalent complications were osteopenia/osteoporosis (22.3%), hypogonadism (10.1%), and primary hypothyroidism (5.3%). In the subgroup multivariate analysis, older age was a risk factor for osteoporosis (Odds ratio: 7.870, 95% CI: 4.729–13.099, $P < 0.001$), hypogonadism (Odds ratio: 6.310, 95% CI: 2.944–13.521, $P < 0.001$), and non-insulin-dependent diabetes mellitus (NIDDM; Odds ratio: 17.67, 95% CI: 2.217–140.968, $P = 0.007$). Splenectomy was a risk factor for osteoporosis (Odds ratio: 1.736, 95% CI: 1.012–2.977, $P = 0.045$). Hydroxyurea was identified as a "protective factor" for NIDDM (Odds ratio: 0.259, 95% CI: 0.074–0.902, $P = 0.034$).

Conclusions To the best of our knowledge, this is the largest cohort of β-TI patients with endocrine disorders evaluated in extremely heterogenic thalassemic populations for age, clinical, hematological, and molecular composition. The study demonstrates that endocrine complications are less common in patients with β-TI compared with β-TM patients. However, regular monitoring with timely diagnosis and proper management is crucial to prevent endocrine complications in β-TI patients.

Keywords Endocrine complications · β-thalassemia intermedia · Prevalence

Introduction

β-thalassemias are a group of hereditary anemias caused by either reduced or complete absence of the production of β-globin chains of the hemoglobin (Hb) tetramer [1]. β-thalassemias are extremely heterogeneous in terms both of genotype and phenotype, depending on the nature of β-gene mutation and the extent of impairment in β-globin chain production. As a rule, heterozygous carriers of β-thalassemia (one affected allele) are asymptomatic and only altered laboratory values are observed. In contrast, the inheritance of two defective β-globin genes results in a wide phenotype spectrum, ranging from transfusion-dependent (thalassemia major [TM]) to mild or moderate anemia (thalassemia intermedia [TI]). β^0 refers to the complete absence of the production of β-globin on the affected allele, β^+ refers to alleles with some residual production of β-globin, and β^{++} to a very mild reduction in β-globin production. TI mutations in both parental genes lead to a moderate reduction in β-globin production. Patients have in general later clinical onset, milder anemia not requiring transfusions for survival during the first few years of life, and quality of life is not severely impaired, but the clinical course of the disease, if remaining

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untreated, is complicated by the multiple effects of chronic hemolytic anemia and the consequent tissue hypoxia, as well as by their compensatory reactions, including increased erythropoiesis with bone marrow expansion and increased intestinal iron absorption [2–7].

Conversely, chronic blood transfusions although are important for anemic patients inevitably lead to iron overload as humans cannot actively remove excess of iron [8–11].

Iron accumulation in β-thalassemia intermedia (β-TI) patients occurs more slowly than in β-TM but can pose a serious risk to the patients' health because complications associated with β-TI may be as serious as those observed in β-TM. However, since patients with β-TI usually have a milder and more slowly progressing phenotype than β-TM patients have, there is a risk that regular monitoring and treatment may be delayed until complications become obvious. Excess iron is extremely toxic to all cells of the body and can cause serious and irreversible organic damage [2, 6, 7].

In patients with β-TM an increased risk for developing several complications, including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadism, and osteoporosis, has been reported, as the patients advance in age, mainly associated with iron overload [12–17].

In view of the limited data available in the literature on endocrinopathies in patients with β-TI, the aim of this multicenter study was to determine the prevalence of endocrine complications in β-TI patients, who were registered in 12 Thalassemia centers of nine countries ($n = 726$), and to evaluate the potential risk factors for endocrine complications in a subgroup of these patients.

Patients and methods

Study design

Our cross-sectional multicountry study included all β-TI patients followed in 2017 at 12 thalassemia centers of Iran, Italy, and Turkey (two centers for each country), and Greece, Oman, Qatar, Jordan, Cyprus, and United Kingdom (one center of each country). Patients' medical history was obtained by review of medical records.

The protocol of the study was approved by Shiraz University of Medical Sciences (Approval code; 1396-01-32-15525). Written informed consent was obtained from the patients or their parents or legal guardian before participation in the study.

Patients' selection

The patients were diagnosed as having β-TI by Hb electrophoresis, complete blood count, clinical history, and in some of them by molecular analysis.

The term β-TI was used to define a type of non-transfusion-dependent thalassemia, with mild genotype and clinical phenotype not requiring regular transfusions for survival. As a rule, the milder cases had no or occasional blood transfusions while the more severe may needed up to 7–8 transfusions annually [12, 18].

The prevalence of registered β-TI patients and endocrine complications of patients were obtained from each center by the data collection form. Moreover, an additional data gathering form was designed to collect more detailed data, including age, sex, Hb and serum ferritin levels, hydroxyurea consumption, and splenectomy. The questionnaire was sent to all participating centers but only six centers: Qatar, Iran (Shiraz, Tehran), Oman, Cyprus, and Jordan were able to fully complete the requested information

The definitions of the endocrine disorders reported by the participating centers are described in Table 1 [19–25].

Statistical analysis

Data were analyzed by SPSS Version 21. Descriptive data were presented as mean, standard deviation, percentage, and prevalence. In the subgroup of TI patients, followed in six centers including Qatar, Iran (Shiraz, Tehran), Oman, Cyprus, and Jordan, information on patient's age, sex, Hb, serum ferritin levels, hydroxyurea therapy, and splenectomy were also available for performing an inferential analysis.

Univariate analysis was done using Chi-square test to determine the relationship of probable risk factors with each registered endocrine disorder. Variables with P value < 0.2 were entered into a multiple logistic regression model with enter method to determine independent factors influencing on the prevalence of endocrine disorders. A two-sided P value < 0.05 was considered statistically significant.

Results

A total of 726 β-TI patients from 12 thalassemia centers from nine different countries were eligible for this study. The highest number of patients were from Iran [414 (57%)]. Overall disease prevalence in patients with β-TI is shown in Fig. 1.

The most common disease-related complications were osteopenia/osteoporosis (22.3%), hypogonadism (10.1%), and primary hypothyroidism (5.3%) (Fig. 1). The prevalence of endocrine disorders in patients with β-TI followed in 2017, in different countries, is presented in Table 2.

Two centers, Greece and Italy, reported the presence of an adrenal mass (3.3% and 1.85%, respectively). In first patient a diagnosis of nonfunctioning adenoma was made

Table 1 Clinical definition of endocrine complications in patients with β-thalassemia intermedia (β-TI)

Complications	Definitions
Diabetes mellitus	The diagnosis of diabetes type 1 or type 2 were made during a period of stable baseline health according to the international guidelines [16, 21].
Osteopenia/osteoporosis	The diagnosis of metabolic bone disease was based on the indications of the International Committee for Standards in Bone Measurements [16, 19].
Hypogonadism	Hypogonadism was defined by the absence of testicular enlargement (<4 ml) in boys, and by the absence of breast development in girls by the age of 16 years. In females, hypogonadism was also defined in presence of hormone replacement therapy (HRT) for failure to proceed through puberty or loss of menses before age 40, and in males in presence of medical prescription of HRT (testosterone or HCG) or by having a serum testosterone concentration lower than established norms for age [20, 24, 25].
Hypothyroidism	Subclinical hypothyroidism was defined as the combination of high TSH with normal FT4 levels. Overt hypothyroidism was defined by the combination of high TSH with low FT4. Central hypothyroidism was defined as low circulating levels of free thyroxin (FT4) in the presence of low to normal TSH levels [16].
Growth hormone deficiency (GHD)	The cutoff limit for the diagnosis of GHD was <3 ng/ml in adults and <10 ng/ml in children and adolescents, using an ultrasensitive chemiluminescence-based immunometric assay. No homogeneous investigations for GHD in adult patients with β-TI were available [16, 23].
Hypoparathyroidism	Hypoparathyroidism was defined as a condition characterized by hypocalcemia and abnormally low or absent PTH levels in patients with normal level of serum magensium [22].
Latent hypocortisolism	Hypoadrenalism was diagnosed when basal morning cortisol was <140 nmol/l (5 µg/dl) [16, 22].

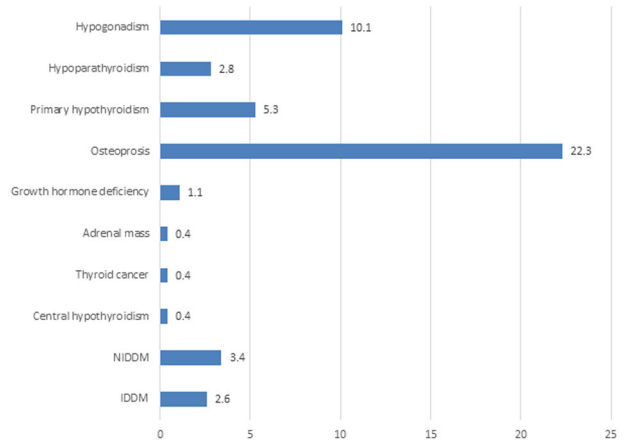

Fig. 1 Overall endocrine disease prevalence (%) in patients with β-thalassemia intermedia. NIDDM non-insulin-dependent diabetes mellitus, IDDM insulin-dependent diabetes mellitus

and in the second patient a myelolipoma (max diameter 3.5 cm) was diagnosed.

No clinical reports of adrenal insufficiency were registered by the participating centers.

In the subgroup of 522 β-TI patients more detailed data were available. The characteristics of these patients are shown in Table 3. The reported mean age of these patients was 30.8 ± 12.1 years (range: 2.5–80 years), with a male-to-female ratio of 1:1. The mean Hb and serum ferritin levels were 9.22 ± 1.21 (6.1–15.1) g/dl and 925 ± 1122 (13–8623) µg/l, respectively.

The highest Hb level reported in one patient was registered after blood transfusions and the lowest serum ferritin level (13 µg/l) relates to a woman with β-TI with iron deficiency, she had 11 pregnancies before the assessment of serum ferritin, requiring oral iron treatment.

The highest prevalence of endocrine disorders in this subgroup of patients was osteopenia/osteoporosis (26.2%), followed by hypogonadism (9.8%), and primary hypothyroidism (5.2%).

Osteopenia/osteoporosis showed significant positive association with age ($P < 0.001$), female gender ($P = 0.047$), lower Hb level ($P = 0.003$), and splenectomy ($P < 0.001$). Hypogonadism was significantly correlated with the older patients' age ($P < 0.001$) and the sex (females) ($P = 0.027$). A significant association with the age ($P = 0.001$) was observed in patients with hypoparathyroidism.

The results of univariate analysis are shown in Table 4. Insulin-dependent diabetes mellitus (IDDM) showed a significant positive correlation with the age ($P < 0.001$), Hb level ($P = 0.025$), and splenectomy ($P = 0.018$). Non-insulin-dependent diabetes mellitus (NIDDM) showed a significant positive correlation with the age ($P = 0.018$) and hydroxyurea consumption ($P = 0.031$).

Finally, multiple logistic regression model was performed. In this model, age was arbitrarily subdivided into two groups: ≤35 and >35 years old. Older age (>35 years old) was associated with an increased risk of osteoporosis (Odds ratio: 7.870, 95% CI: 4.729–13.099, $P < 0.001$), hypogonadism (Odds ratio: 6.310, 95% CI: 2.944–13.521, $P < 0.001$), and NIDDM (Odds ratio: 17.67, 95% CI: 2.217–140.968, $P = 0.007$). An increased risk of osteopenia/osteoporosis was associated with splenectomy (Odds ratio: 1.736, 95% CI: 1.012–2.977, $P = 0.045$). On the contrary, hydroxyurea consumption resulted a "protective

Table 2 Prevalence of endocrine disorders in patients with beta-thalassemia intermedia (β-TI) in different countries

Country, number of patients, % and endocrine complications	IDDM	NDDM	Central hypothyroidism	Thyroid cancer	Adrenal mass	Growth hormone deficiency	Osteopenia/ osteoporosis	Primary hypothyroidism	Hypoparathyroidism	Hypogonadism
Cyprus $n = 15$	0	2 (13.3)	0	0	0	0	2 (13.3)	1 (6.6)	0	1 (6.6)
Greece $n = 60$	2 (3.3)	4 (6.6)	0	2 (3.3)	2 (3.3)	0	11 (18.3)	8 (13.3)	3 (5)	12 (20)
Iran $n = 414$	13 (3.1)	6 (1.4)	0 –	1 (0.2)	0 –	0 –	110 (26.5)	22 (5.3)	9 (2.1)	42 (10.1)
Italy $n = 69$	0	1 (1.4)	0	0	1 (1.4)	0	0	2 (2.8)	0	5 (7.2)
Jordan $n = 16$	0	1 (6.2)	0	0	0	0	3 (18.7)	0	1 (6.2)	4 (25)
Oman $n = 49$	0	3 (6.1)	0	0	0	0	18 (36.7)	3 (6.1)	1 (2)	4 (8.1)
Qatar $n = 28$	1 (3.5)	6 (21.4)	0	0	0	5 (17.8)	4 (14.2)	1 (3.5)	0	0
Turkey $n = 69$	1 (1.4)	0 –	3 (4.3)	0 –	0 –	1 (1.4)	9 (13.0)	0 –	6 (8.6)	1 (1.4)
United Kingdom $n = 6$	2 (33.3)	2 (33.3)	0	0	0	2 (33.3)	5 (83.3)	2 (33.3)	1 (16.6)	2 (83.3)

IDDM insulin-dependent diabetes mellitus, *NIDDM* non-insulin-dependent diabetes mellitus

Table 3 Patient's and disease characteristics of the subgroup study population ($n = 522$)

Parameter	Frequency, no. (%)
Age, years	
<18	63 (12.1)
18–35	290 (55.6)
>35	169 (32.4)
Male/female	260 (49.8)/262 (50.2)
Splenectomized	228 (43.7)
Serum ferritin, μg/l	
≤1000	405 (77.6)
>1000	116 (22.2)
Hemoglobin, g/dl	
<9	240 (46)
≥9	273 (52.3)
Hydroxyurea treatment	350 (67)
Complications	
Osteopenia/osteoporosis	137 (26.2)
Hypogonadism	51 (9.8)
Primary hypothyroidism	27 (5.2)
Non-insulin-dependent diabetes mellitus (NIDDM)	18 (3.4)
Insulin-dependent diabetes mellitus (IDDM)	13 (2.5)
Hypoparathyroidism	11 (2.1)
Thyroid cancer	1 (0.2)

In data collection, we had some missing information regarding serum ferritin and serum hemoglobin levels, splenectomy, and hydroxyurea consumption

factor" for NIDDM (Odds ratio: 0.259, 95% CI: 0.074–0.902, $P = 0.034$) (Table 5).

It was not possible to perform a multivariate analysis for IDDM ($n = 13$) and hypoparathyroidism ($n = 11$) due to small number of patients present in our survey.

Discussion

Patients with β-TI experience with aging many clinical complications despite their independence from frequent transfusions. The main causes of endocrine disorders in β-TI are anemia, caused by ineffective erythropoiesis, relative bone marrow hyperactivity, medullary expansion, extramedullary hyperplasia, and iron overload [12].

Our results show that osteopenia/osteoporosis is the most common complication in the 3rd–5th decades of life, which is in agreement with the Optimal Care Study (OCS) reported by Taher et al. (~22%) [10]. The etiology of bone mineral loss is multifactorial. Medullary expansion due to anemia, patient age, duration of the disease, vitamin D deficiency, hypogonadism, and other endocrine-associated

Table 4 Univariate analysis of covariates of endocrine disorders in the subgroup population ($n = 522$)

	IDDM $n = 13$	NIDDM $n = 18$	Primary HPT $n = 27$	Osteopenia/ osteoporosis $n = 137$	HPT $n = 11$	HH $n = 51$
Age, years						
≤35 ($n = 352$)	0.0	2	4.6	10.5	0.6	3.1
>35 ($n = 170$)	7.7	6.5	6.5	59.5	5.4	24.4
P value	<0.001*	0.018*	0.400	<0.001*	0.001*	<0.001*
Sex						
Male ($n = 260$)	1.5	2.7	6.6	22.3	2.1	7.2
Female ($n = 262$)	3.5	4.2	3.8	30.2	2.4	13.3
P value	0.261	0.473	0.169	0.047*	1.000	0.027*
Hemoglobin, g/dl						
<9 ($n = 240$)	0.8	4.2	6.8	32.5	2.3	9.4
≥9 ($n = 273$)	4.0	2.9	3.7	20.5	2.2	11.4
P value	0.025*	0.480	0.157	0.003*	1.000	0.551
Splenectomy						
No ($n = 159$)	0.6	6.3	4.5	20.1	3	9.2
Yes ($n = 228$)	5.3	3.5	6.2	44.7	3.1	17.2
P value	0.018*	0.227	0.649	<0.001*	1.000	0.041*
Hydroxyurea treatment						
No ($n = 76$)	1.4	6.6	5.3	34.2	4	10.7
Yes ($n = 350$)	3.4	1.7	5.4	30.2	2.3	12.3
P value	0.481	0. 031*	1.000	0.496	0.420	0.845
Ferritin, µg/l						
≤1000 ($n = 405$)	2.5	2.7	4.5	25.3	1.8	9.5
>1000 ($n = 116$)	2.6	6.1	8.0	30.4	4.3	14.1
P value	1.000	0.088	0.152	0.282	0.133	0.188

All data except *P* values are presented as percentage. In data collection, we had some missing information regarding serum ferritin and serum hemoglobin levels, splenectomy, and hydroxyurea consumption

IDDM insulin-dependent diabetes mellitus, *NIDDM* non-insulin-dependent diabetes mellitus, *HT* hypothyroidism, *HPT* hypoparathyroidism, *HH* hypogonadotropic hypogonadism

*P values < 0.05 were considered as statistically significant

complications are significant contributory factors. Therefore, an annual screening for osteoporosis/osteopenia, after the second decade of life, is recommended. Although bisphosphonates remain the gold standard of osteoporosis [5]; the most beneficial effects for the treatment of low bone mass in thalassemia has yet to be established and needs to be considered in future prospective studies.

The second most common complication found was secondary hypogonadism, although the frequency in our study was lower compared with OCS study (10.1% vs.17.3%), followed by IDDM (6% vs. 1.7%) [10]. The prevalence of primary hypothyroidism was confirmed to be similar in both studies (~5%) [10]. The variable prevalence of endocrine complications reported in these two studies could be due to different severity of anemia, iron overload, patients' age and gender.

In fact, in our subgroup of patients, older age was significantly associated with almost all complications including IDDM, NIDDM, osteopenia/osteoporosis, hypoparathyroidism, and hypogonadism.

In univariate analysis, IDDM was significantly associated with higher Hb levels and splenectomy. However, this association was not confirmed with a multivariate analysis, probably due to small sample size of patients with IDDM.

Female gender was significantly associated with osteopenia/osteoporosis and hypogonadism. Furthermore, hypogonadism was also significantly associated with splenectomy.

In brief, these findings reinforce the importance of regular follow-up of patients with β-TI for early detection and management of associated complications.

In general, when we compared β-TI patients with those with β-TM [13, 26, 27] a lower prevalence of endocrine complications was observed. We believe that, although the prevalence of endocrinopathies in β-TI tend to increase with age, it may be attributed to the lower extent, favorable genotype, slower rate, and hepatic predominance of iron loading in this group of patients. Nevertheless, a regular assessment of serum ferritin levels and T2* MRI of heart and liver, if available, are recommended for a prevention of endocrine complications secondary to iron overload. As reported in the literature, although serum ferritin is much less accurate and is weakly correlated with degree of siderosis, its monthly measurement could still have some value in predicting endocrine complications [28–30]. It has

Table 5 Multivariate analysis for determination of complication rate in the subgroup population ($n = 522$)

Complication/parameter	Regression coefficient	Odds ratio	95% CI	*P* value
Osteoporosis				
Male	−0.317	0.690	0.421–1.132	0.142
Hemoglobin ≥ 9 g/dl	−0.401	0.494	0.903–2.471	0.118
Age > 35	2.063	7.870	4.729–13.099	<0.001*
Splenectomized	0.551	1.736	1.012–2.977	0.045*
Constant	−2.023	0.132		<0.001
Non-insulin-dependent diabetes mellitus (NIDDM)				
Age > 35	2.872	17.677	2.217–140.968	0.007*
Hydroxyurea treatment	−1.352	0.259	0.074–0.902	0.034*
Ferritin > 1000 µg/l	0.321	1.379	0.340–5.591	0.653
Constant	−4.717	0.009		<0.001
Primary hypothyroidism				
Ferritin > 1000 µg/l	0.314	1.368	0.554–3.377	0.496
Male	0.475	1.609	0.710–3.643	0.254
Hemoglobin ≥ 9 g/dl	−0.542	0.581	0.250–1.352	0.208
Constant	−3.011	0.049		<0.001
Hypogonadism				
Male	−0.649	0.522	0.272–1.001	0.050
Age > 35	1.842	6.310	2.944–13.521	<0.001*
Splenectomized	0.144	1.155	0.546–2.442	0.707
Constant	−2.744	0.064		<0.001

*P values < 0.05 were considered as statistically significant

been also recommended that iron chelation therapy should be started if serum ferritin is above 500–800 µg/l or the liver iron concentration is above 5 mg/g dry weight [29, 30].

We recognize that one limit of our study is the heterogeneity of patients enrolled in the survey, the different severity of iron overload assessed by serum ferritin level (925 ± 1122 µg/l), and the lack of full information reported by some participating centers. As reported, in β-TM patients the prevalence of endocrine complications is quite variable in different countries [11.13–1722.26]. Various explanations have been reported in the current literature, but this aspect needs to be investigated furtherly in subjects with β-TI.

Nevertheless, our study report a wider view on the prevalence of endocrine and nonendocrine (osteopenia/osteoporosis) complications in a large cohort of patients with β-TI, and stimulates the attention for the development of further studies in order to assess the impact of anemia, frequency of transfusions, iron chelation therapy, splenectomy and hydroxyurea treatment on the outcome of these patients.

Finally, our study confirm that although endocrine complications are less common in patients with β-TI compared with data reported in the literature in β-TM patients. Nevertheless a regular monitoring with timely diagnosis and proper management is recommended to optimize the quality of life of these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol of the study was approved by Shiraz University of Medical Sciences (Approval code: 1396-01-32-15525).

Informed consent Written informed consent was obtained from the patients or their parents or legal guardian before participation in the study.

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