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Prevalence of Endocrinopathies in Beta Thalassemia Major Patients attending Al-Faihaa Specialized Endocrine Center at Al-Basra City

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Abstract. Background: Endocrine disorders in patients with thalassemia are one of the most common complications, and the burden of excessive iron overload and suboptimal chelation therapy mainly causes them. The prevalence is very high; however, determining it is almost impossible due to the wide range of heterogeneity among people and the varying times of exposure to chelation agents. Aim: To find out the prevalence of endocrinopathies and their types among patients with Beta-thalassemia major. Patients and Method: A retrospective descriptive cross-sectional study, in which the data of 172 thalassemia major patients who consulted the AL-Faihaa Specialized Endocrine, Metabolism and Diabetes Center (FSEMD) during the period from the first of September 2008 to the first of July 2017, were analyzed, and the results were obtained. Results: The study showed that out of 172 patients with Beta-thalassemia major, endocrinopathies were reported in 165 (95.9%) of them. Growth hormone (GH) deficiency, secondary Hypoparathyroidism, non-insulin-dependent diabetes mellitus (NIDDM), and hypogonadism were the commonest endocrine complications. Age of the patient and duration of disease were primary risk factors significantly affecting the prevalence of these complications.

Highlights :

1. High Prevalence of Endocrinopathies: 95.9% of Beta-thalassemia major patients had at least one form of endocrine disorder, indicating it as a major complication.
2. Common Types Identified: Growth hormone deficiency, secondary hypoparathyroidism, non-insulin-dependent diabetes mellitus, and hypogonadism were the most frequent endocrinopathies.
3. Risk Factors: Older age and longer disease duration were significantly associated with a higher prevalence of these endocrine complications.

Keywords: Prevalence, Endocrinopathies, Beta Thalassemia Major

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Introduction

A. β-thalassemia

It is the result of an inherited defect in the synthesis of beta chains of hemoglobin, leading to either reduced (B+) or absent (B0) B-chain. There are more than 200 different mutations, most of which come from the defective expression of the B-globin gene [1].

B. Classification of β-thalassemias

1. B-thalassemia Major (BTM)

   Which is the severe transfusion-dependent form (TDT), in which the mutation results in complete absence of B-Chain (B0). It is also known as Cooley's Anemia [2] . Patients with BTM who are untreated or poorly treated are characterizing by growth retardation, pallor, poor musculature tone, jaundice, leg ulcers, genu valgum, hepatosplenomegaly, masses from extramedullary hematopoiesis and skeletal changes due to bone marrow expansion [2]. These involved deformities in the long bones of the legs with craniofacial changes as bossing of the skull, prominent malar eminence, nasal bridge depression, a mongoloid slanted eye, and hypertrophy of the maxillae, that resulted in exposing of the upper teeth [2]. If a regular blood transfusion regimen is initiated early, most of these complications can be prevented or delayed [3]. On the other hand, treatment regimens had its owned sequels, where the transfused patients may have complications due to iron overload like growth retardation, endocrine dysfunction, live fibrosis, dilated cardiomyopathy and arrhythmia [3]. Other complications are hypersplenism, chronic hepatitis B and C, HIV infection, venous thrombosis, and osteoporosis. The risk for hepatocellular carcinoma is also rising in patients with viral liver diseases and iron overload [3].

2. B-thalassemia Minor

   Here, the affected individuals are either symptomless with normal hematological parameters or present with mild anemia [4].

3. B-thalassemia Intermedia (TI)

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Patients with TI usually presented at an older age than those with BTM (at 2 to 6 years of life). They have mild anemia and often do not require regular blood transfusions. However, growth and development are also delayed [5].

C. Treatment of β-thalassemia Major

1. Blood Transfusion

Patients with BTM need regular lifelong blood transfusions, where the real aim is to keep the pre-transfusion hemoglobin level more than 9 - 10.5 g/dl to [6]:

a. Prevent the complications of chronic anemia and ineffective erythropoiesis.
b. Ensure healthy growth and development through childhood.
c. Extend survival in BTM patients as possible [6].

2. Iron Chelating Drugs

a. Desferrioxamine (Deferoxamine, Desferal or DFO)

It is the gold standard iron chelation therapy. It acts by reducing iron overload through the promotion of iron excretion in urine and stool [7]. About one-half to two-thirds of the iron is excreted in the urine, and the rest in the stool. It is recommended to be used when the serum ferritin level is (≥ 1000 ng/ml) or after (10-20) blood transfusions [7].

b. Splenectomy

The most significant indications for splenectomy include progressive splenomegaly, an increase in blood requirements. Where annual transfusion needs exceed 220 ml/kg/year, it is best to avoid for at least beyond the age of 5 years, because of the increased risk of infection [7].

3. Bone Marrow Transplantation

It can be carried out by using sibling donor HLA-matched transplants that will give a good prognosis if executed early in life [8].

D. Complications of β-thalassemia Major

1. Iron Overload

This iron overload would destroy the endocrine glands, pancreas, liver, and the myocardium of the heart when those patients around to reach adolescence [9].

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2. Cardiac Complications

They are a major determinant of survival among this population [10].

3. Liver Complications

Liver diseases are recorded as the second leading cause of death in thalassemia patients, where if hepatomegaly started before the initiation of transfusion therapy in patients who are severely affected, is almost secondary to extramedullary hematopoiesis [11].

4. Splenomegaly and Hypersplenism

RBCs and other blood elements may be tricked in the hyperactivated spleen, resulting in anemia, thrombocytopenia in addition to some extent of neutropenia. The enlarged spleen may also cause physical discomfort in such patients [12].

5. Thromboembolic Complications

β-thalassemia patients are at significant risk to have one or more of thromboembolic events, as pulmonary embolism [13].

6. Bone Complications

Thinning of the vertebrae and long bones' cortex secondary to ineffective erythropoiesis and erythroid marrow expansion may result in pathologic fractures of long bones [9].

7. Infections

The most common infections in such a patient group are the blood-borne infections, like hepatitis B and C, HIV, and malaria [10, 11].

8. Endocrine Complications

a. Growth Retardation

Retardation of growth in Thalassemic children is a common feature and happened Approximately in all age periods (infantile, pre-pubertal and the pubertal) [14].

This retardation due to many factors affects normal growth. Pituitary iron deposition affects growth hormone secretion, sex steroids, and bone disease [15]. A significant cause of growth retardation is Malnutrition in Children who had thalassemia who lives in poor areas because of inadequate

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nutrient intake of zinc and others essential amino acids and vitamins [16]. growth failure rates in those individuals were higher once fifteen years of age because of hypogonadism and growth spurt absent [17].

b. Delayed Puberty and Hypogonadism

They are one of the most common endocrine disorders secondary to iron overload. Hypogonadism in adult BTM patients is quite common, with a prevalence of 40-60%. Hypogonadism could be either primary as a result of iron accumulation in the gonads or, which is more common, secondary (hypogonadotropic) hypogonadism because of hemosiderosis of gonadotrophic cells that are located in the anterior pituitary gland [18].

c. Diabetes Mellitus and Impaired Glucose Tolerance

The pathogenesis of diabetes in thalassemia patients is mainly due to impaired insulin secretion due to chronic iron deposition in the pancreas [18], with particular immune system activation against pancreatic β-cells resulting in cell damage [19], and death secondary to fat transformation [20].

d. Hypothyroidism

Hypothyroid (primary) or pituitary (secondary) in thalassemia major may be due to deposition of iron in the thyroid or pituitary, respectively, and its complications, such as lipid peroxidation, free radicals release, and oxidative stress, but the exact mechanism is not well-known [21].

Materials and Methods

A. Study Design and Place of the Study

A cross-sectional retrospective descriptive study was carried out at Al Faihaa Specialized Diabetes, Endocrine and Metabolism Center (FSDEM) in Basra city, which included all patients who were referred from the Basra Hematology center, outpatient clinics of other hospitals, and who were diagnosed with thalassemia major.

1. The Study Population

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All TM patients who had been kept on regular blood transfusion and chelation therapy were evaluated retrospectively, depending on their electronically recorded data at the FSDEM center for growth, pubertal status, and other endocrine functions. They had been investigated by oral glucose tolerance test, calcium, phosphate, alkaline phosphatase, vitamin D, thyroid profile, and parathyroid hormone. Those with delayed or arrested puberty, sex steroids, and gonadotropins had also been checked. The glucagon stimulation test was assessed in patients with height ≤−3 SD.

2. The Inclusion Criteria Include

Registered thalassemia major patients from the date of 1st September 2008 tile 30th of July 2017, aged haemosiderosis years and above, on frequent blood transfusion one or more per month, using chelation therapy and s. Ferntine more than 1000 mg was included in this study

3. The Exclusion Criteria Include

Any patient who had a history of congenital or similar familial endocrine disorder (except for diabetes), previous endocrine gland injury or surgery, and inadequate information was excluded from the study. A hundred eighty-eight patients were included in our study; 16 patients were excluded because of a lack of adequate information or having other associated hemoglobinopathies, 7 patients had no complications at the time of registration, and the remaining 165 patients fulfilled the inclusion criteria of our designated study.

B. Data Collection

Clinical, axiological, hormonal, and biochemical data from the initial screening visits of all TM patients who attended the FSDEM center were collected from the clinic charts and electronic database; then they were used to calculate the prevalence of endocrinopathies. When the initial hormonal results were inconclusive, the results from the follow-up visits were used to confirm the existence of endocrinopathies. Other information, such as demographic data, was used to identify risk factors for developing endocrinopathies. The frequency of growth/endocrine dysfunction in

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patients aged ten years or less was compared to the rest of the group to analyze whether the screening in the first decade of life was justified.

C. Statistical Analyses

Statistical analysis of the data was carried out using the SPSS program (Statistical Package for Social Science version 17.0). The results were then tabulated. Chi-square and Fisher's Exact tests were used to detect if there is an association between different variables. The association was considered to be significant when the P-value was less than 0.05. The Excel program has also been used to display the results in graphic figures.

Results

A. The Sociodemographic Distribution of Patients Enrolled in This Study Was Summarized in Table 1

Table 1. Sociodemographic Distribution of Patients

Sociodemographic Feature	Number /Percent
Sex	
Male	85/49.4%
Female	87/50.6%
Age	
Mean ±SD/years	12.5-+ 4.8
Range	3-29 years
Less than 10	48 / 27.9%
10-19 years	111 / 64.5%
20-+years	13 / 7.6%
Marital status	
Single	168/ 97.7%
Married	4/ 2.3%
Occupation	

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Employed	16/9.3%
Not employed	42/24.4%
Students	96/55.8%
Child/pre-school age	18/10.5%
Place of living	
City center	76/44.2%
Rural area	96/55.8%
Social class	
Low	129/75%
Middle	43/25%
High	00/00

To assess the nutritional status and growth pattern of the involved patients in this designated study, their body mass index BMI was taken as a parameter. When plotting BMI on the reference that was adapted for the same age and sex by the WHO, we found that out of 11 adult patients who were older than 20 years, five patients (45.5%) were underweight, and 54.5% were within the normal range. No overweight or obese patient was identified, as shown in Table 2.

Table 2. Description of Adult Patients according to their BMI

BMI FOR ADULT	**Frequency**	**Percent**
Underweight (<18.5)	5	45.5%
Normal (18.5-24.9)	6	54.5%
Overweight (25-29.9)	0	0.0%

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Obese (30 and more)	0	0.0%
Total number of adults	11	100%

Regarding the children and adolescent patients, who constitute 161 from the total 172 patients (aged 2-20 year), the results displayed that 32 of them were underweight (19.8%), 118 (73.2%) within normal range, 8 (4.7%) at risk of overweight and only 3 (1.8%) were obese.

Table 3. Description of Patients Aged 2- 20 Years Old according to their BMI

BMI for children	Frequency	Percent
5^{th} (underweight)<	32	19.8%
5^{th}-84.9^{th}(standard)	118	73.2%
85^{th}-94.9^{th} (risk of overweight)	8	4.9%
95^{th} and more (overweight)	3	1.8%
Total number of children and adolescents	161	100%

To clarify if there is an effect for the duration of the disease and exposure to the treatment regime (regular blood transfusion and chelating therapy), we classified the duration of their illness and receiving treatment into categories; the results are shown in Table 4

Table 4. Distribution of Patients According to the Duration of the Disease

Duration of disease	Frequency	Percent
Less than ten years	69	40.1%
10-14 years	74	43.0%
15-19 years	20	11.6%

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20 years or more	09	5.2%
Total	172	100%

On the other hand, the analysis of data to assess the endocrine complications in the involved TM patients had shown that the most common endocrine complications were Growth hormone deficiency (43.6%). Followed by secondary Hypoparathyroidism (13.4%), noninsulin-dependent diabetes mellitus (9.9%), Hypogonadism (8.7%), Primary hypothyroidism (7%), insulin-dependent diabetes mellitus IDDM (4.7%), Primary Hypoparathyroidism (1.7%), and finally, Adrenal insufficiency (1.2%). Table 5-

Table 5. Patient Distribution According to the Type of Endocrine Complication that They Had.

Type of Endocrinopathies	Number of cases	Percent%
Growth hormone deficiency	75	43.6%
Secondary Hypoparathyroidism	23	13.4%
Non-Insulin Dependent DM	17	9.9%
Hypogonadism	15	8.7%
Primary Hypothyroidism	12	7%
Insulin Dependent DM	8	4.7%
Primary Hypoparathyroidism	3	1.7%
Adrenal Insufficiency	2	1.2%

To estimate the relationship between the different study variables and the type of endocrinopathies the patients had, we compare to show that. The results presented in Table 6

Table 6. Comparison of the Type of Endocrinopathies and The Socio-Demographic Characteristics.

Socio-Demographics Features	GH Deficiency Number/percent	Secondary Hypoparathyroidism Number/percent	NIDDM Number/Percent	Hypogonadism Number/percent

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Sex				
Male	37 (21.5%)	9 (5.2%)	8 (4.7%)	5 (2.9%)
Female	38 (22.1%)	14 (8.1%)	9 (5.2%)	10 (5.8%)
	p-value 0.553	p-value 0.102	p-value 0.520	p-value 0.094
Age /years				
Less than 10	16 (9.3%)	7 (4.1%)	1 (0.6%)	0
10-19	57 (33.1%)	12 (7%)	13 (7.6%)	12 (7%)
20- +	2 (1.2%)	4 (2.3%)	3 (1.7%)	3 (1.7%)
	P-value 0.011	P-value 0.110	p-value 0.031	p-value 0.003
Marital status				
Single	75 (43.6%)	23 (13.4%)	15 (8.7%)	14(8.1%)
married	0	0	2 (1.2%)	1 (0.6%)
	p-value 0.098	p-value 0.560	p-value 0.049	P-value 0.308
Social class				
Low	52 (30.2%)	15 (8.7%)	13 (7.6%)	12 (7%)
Middle				
High	23 (13.3%)	8 (4.7%)	4 (2.3%)	3 (1.7%)
	0	0	0	0
	p-value 0.046	p-value 0.100	p-value 0.574	p-value 0.456
Occupation				
Employed	7 (4.1%)	3 (1.7%)	4 (2.3%)	3 (1.7%)
Not employed	18 (10.5%)	5 (2.9%)	6 (3.5%)	9 (4.7%)
Students	45 (26.2%)	11 (6.4%)	7 (4.1%)	3 (1.7%)
Child	5 (2.9%)	4 (2.3%)	0	0
	p-value 0.068	p-value 0.489	p-value 0.051	p-value 0.001
Place of residence				
City Centre	39 (22.7%)	10 (5.8%)	9 (5.2%)	4 (2.3%)
Rural areas	36 (20.9%)	13 (7.6%)	8 (4.7%)	11 (604%)
	P-value 0.024	p-value 0.178	p-value 0.151	p-value 0.081
Duration of disease and treatment				
Less than 10	27 (15.7%)	12 (7%)	2 (1.2%)	0
10-14	39 (22.7%)	6 (3.5%)	8 (4.7%)	8 (4.7%)
	8 (4.7%)	3 (1.7%)	4 (2.3%)	5 (2.9%)

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15-19 20 +	1 (0.6%) p- value 0.070	2 (1.2%) p-value 0.236	3 (1.7%) p-value 0.006	2 (1.2%) p-value 0.004
Family history of diabetes Negative Positive	 52 (30.2%) 23 (13.4%) p-value 0.123	 15 (8.7%) 8 (4.7%) p-value 0.152	 11 (6.4%) 6 (3.5%) p-value 0.366	 9 (5.2%) 6 (3.5%) p-value 0.243

Socio-demographics features	**Primary hypothyroidism Number/percent**	**IDDM Number/percent**	**Primary Hypoparathyroidism Number/percent**	**Adrenal insufficiency Number/percent**
Sex Male Female	 7 (4.1%) 5 (2.9%) p-value 0.367	 1 (0.6%) 7 (4.1%) p-value 0.034	 1 (0.6%) 2 (1.2%) p-value 0.509	 2 (1.2%) 0 p-value 0.243
Age /years Less than 10 10-19 20- +	 2 (1.2%) 7 (4.1%) 3 (1.7%) p-value 0.081	 2 (1.2%) 4 (2.3%) 2 (1.2%) p-value 0.207	 0 3 (1.7%) 0 p-value 0.648	 1 (0.6%) 0 1 (0.6%) p-value 0.048
Marital status Single married	 12 (7%) 0 p-value 0.717	 7 (4.1%) 1 (0.6%) p-value 0.175	 3 (1.7%) 0 p-value 0.931	 2 (1.2%) 0 p-value 0.954
Social class Low Middle High	 11(6.4%) 1(0.6%) 0 p-value 0.149	 7 (4.1%) 1 (0.6%) 0 p-value 0.362	 2 (1.2%) 1 (0.6%) 0 p-value 0.581	 2 (1.2%) 0 0 p-value 0.561
Occupation Employed Not employed Students Child	 1 (0.6%) 5 (2.9%) 5 (2.9%) 1 (0.6%) p-value 0.538	 0 3 (1.7%) 4 (2.3%) 1 (0.6%) p-value 0.655	 0 1 (0.6%) 2 (1.2%) 0 p-value 1.000	 1 (0.6%) 0 1 (0.6%) 0 p-value 0.298

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Place of residence				
City Centre	6 (3.5%)	3 (1.7%)	1 (0.6%)	1 (0.6%)
Rural areas	6 (305%)	5 (2.9%)	2 (1.2%)	1 (0.6%)
	p-value 0.214	p-value 0.495	p-value 0.587	p-value 0.690
Duration of disease and treatment				
Less than 10	3 (1.7%)	3 (1.7%)	1 (0.6%)	1 (0.6%)
10-14	4 (2.3%)	2 (1.2%)	1 (0.6%)	0
15-19	2 (1.2%)	1 (0.6%)	1 (0.6%)	0
20 +	3 (1.7%)	2 (1.2%)	0	1 (0.6%)
	p-value 0.033	p-value 0.100	p-value 0.568	p-value 0.070
Family history of diabetes				
	10 (5.8%)	4 (2.3%)	0	2 (1.2%)
Negative	2 (1.2%)	4 (2.3%)	3 (1.7%)	0
Positive	p-value 0.267	p-value 0.173	p-value 0.024	p-value 0.502

Table 7 shows the most significant variables in this study that affect the prevalence of endocrine complications in TM patients.

Table 7. The Most Important Involved Variables that Influence the Incidence of Endocrine Complications in TM Patients

Variables not in the Equation	Score	Degree of freedom (df)	Significance
Age	9.117	1	0.003
Gender	0.126	1	0.723
Duration of disease	9.094	1	0.003
Overall statistics	9.174	3	.027
Family history of diabetes mellitus	0.773	1	0.379
Overall statistic	0.773	1	0.379

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As shown in Table 8, 67.4% of enrolled patients had at least one endocrinopathy, while the remaining 27.5% had more than one.

Table 8. The distribution of patients according to the number of endocrine complications they have

Variable Type	Frequency	Percent%
Patients with at least one endocrinopathy	93	67.4%
Patients with more than one endocrinopathy	38	27.5%
Patients with no endocrinopathies	7	5.1%
Total	138	100%

Finally, during the data analysis process, we identified other complications unrelated directly to thalassemia as short stature secondary to many other causes (nutritional, familial, idiopathic, etc), rather than growth hormone deficiency. Table 9.

Table 9. Distribution of Patients with Endocrinopathies not Related to Thalassemia

Growth Retardation due to other causes	**Frequency**	**Percent%**
Yes	57	33.1%
NO	115	66.9%

Discussion

Thalassemia major is a common inherited hematological problem all over the world, particularly in the Mediterranean areas, including our country [22] [23]. The risk of having endocrinopathies among TM patients has been reported in many studies [24]. The study showed that among 172 TM patients registered in the AL-FSDEM center recording system, 165 (95.9%) patients were found to have endocrinopathies, indicating that the risk of such complications is high among TM patients, which necessitates the importance of early screening for these problems in any patients with thalassemia major. Our results are similar to those of other studies [25] [26] [27]. In the present work, both sexes were affected with a statistically insignificant difference (p-value 0.723). It

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has shown that 64.5% of patients were 10-19 years old, which indicate that endocrinopathies need time to occur as the thalassemia is a hemolytic disease and its' treatment with frequent blood transfusion resulting in iron over loud with its' subsequent precipitation in vital body organs like endocrine glands that lead to endocrinopathies. The same results were similarly reported by other studies [28] [29] [30] [31].

Also, 97.7% of patients were single, and 9.3% were employed (Table 1), both findings possibly attributed to their illness and the resulting poor psychological and physical fitness. These results are consistent with other studies [32] [33] [34] [35], which mention that the majority of the studies are single.

Moreover, over 55.8% of registered patients were living in rural areas, and 75% of them were of low socioeconomic status. These results are consistent with other studies [36] [37] [38] , which mention that the majority of the studies are single. These results are due to irregular consultation for medical advice and follow-up, improper intake of chelating agents because of their poverty, and a fear of specialized centers, in addition to increased consanguineous marriages in those families.

The results of this study revealed that (45.5%), (19.8%) of adult patients and children, respectively, were underweight, while the majority (75%) of children and adolescents, versus (54.5%) of the adults, were within the normal range. From these results, it seems that the disease starts to affect the growth of patients with increasing age due to the development of its complications as the patient grows older. The growth failure is thought to be multifactorial, where the contributing factors to stunted growth in TM patients may include chronic anemia, transfusion iron overload, hypersplenism, and chelation toxicity, in addition to GH deficiency/insufficiency, hypogonadism, hypothyroidism, chronic liver disease, zinc deficiency, undernutrition, and psychosocial stress [39] [40].

Regarding the relation between the disease duration and the prevalence of endocrinopathies, it has been found that 40.1%, 43% were less than ten years and 10-14 years, respectively, after which the incidence of endocrine complications declined. It can explain that patients who were suffering from the disease for more than 15 years were possibly lost due to disease complications where they either crippled or died. These results are consistence with those of other published studies [41].

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Although the study showed that the majority (67.4%) of our patients have at least one endocrinopathy, the most common endocrinopathy encountered in TM patients was Growth hormone deficiency. Where it was reported in 43.6% of patients, followed by secondary Hypoparathyroidism, NIDDM, and Hypogonadism in 13.4%, 9.9%, and 8.9%, respectively, indicated that all endocrinopathies could complicate thalassemia major. In reviewing the literature and related studies, it seems that our results are not far from those of other studies. However, the frequent occurrence of endocrine complications may differ in different studies, where hypogonadism and diabetes were reported to be the commonest endocrine complications [42] [43] [44]

Conclusions

1. Endocrinopathies are a common complication, as reported in 95.9% of the cases
2. Growth hormone deficiency, secondary Hypoparathyroidism, NIDDM, and Hypogonadism are the most common endocrine complications.
3. Age of patients and durations of disease significantly affect the prevalence of endocrinopathies among patients with thalassemia major.

Recommendations

1. For achieving better health care and to prevent the risk of endocrine complications and patients' co-morbidities, early screening and strict follow up even for defaulted patients, is recommended.
2. A more detailed recording system for all patients with thalassemia is an essential step in the disease control and management
3. Educational programs for both patients and their families about the risk of complications and better outcomes of disease control are recommended at different levels of the health care system.
4. Multicentre scientific teamwork, including all concerned related specialties with sharing experience and relevant data, is a mandatory step for successful management of patients with this miserable disease and to improve their life quality.

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Ethical Approval: The agreement of the Basrah health directorate and the endocrine department of Al-Faihaa Specialized Endocrine Center at Al-Basrah city authority, all patient was informed and agreed to participate in the study.

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