Endocrine Complications and the Effect of Compliance to Chelation Therapy in Patients with Beta Thalassemia Major in Eastern Province of Saudi Arabia

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Abstract

Background: Endocrinopathies and metabolic complications are common in Beta Thalassemia major patients receiving blood transfusion. Chelation therapy has a role in preventing or delaying such complications. However, patients may face difficulties to adhere with chelation therapy due to several reasons.

Aim: To evaluate endocrine complications in beta thalassemia major patients (2-30 years) in The Eastern Province of Saudi Arabia and compare the onset of endocrine complications among compliant and non-compliant patients. Moreover, assess the barriers that hinder the compliance on chelating therapy.

Methods: A Cross-sectional study was conducted on 89 patients (43 male and 46 females) in patients aged 2 to 30 years attending different hospitals in the Eastern province of Saudi Arabia. A semi-structured questionnaire was used to collect demographic data, medical histories. The questionnaires were filled by face-to-face interviews with the patients, or their care givers and the required laboratory data was retrieved from the medical records of patients.

Results: The most prevalent abnormality was underweight detected in (40.9 %) of patients followed by subclinical hypothyroidism (37.7 %), short stature (35.2 %), hypothyroidism in (17.0 %) and diabetes mellitus in (13.6 %). Significant difference between those who are compliant to iron chelation therapy and those who are not in terms of the prevalence of short stature *(P value= .05)* and hypothyroidism *(P value= .05)* being the most evident. Percentage of Patients who were not compliant on taking chelation therapy is (21.6 %) and (9.1 %) of patients were not taking them at all.

Conclusion: Despite the role of chelation therapy in the management of iron overload, the risk of secondary endocrine and metabolic complications remained considerable. Subclinical hypothyroidism and short stature were the most frequent endocrine complications encountered in this study.

Introduction

Beta-thalassemia is a group of hereditary blood disorders, characterized by anomalies in the synthesis of the beta chains of hemoglobin.[1] These anomalies result in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Beta thalassemia (“β-thal”) is classified into three forms depending on the severity of symptoms: thalassemia trait, thalassemia minor and thalassemia major. Among the three forms of thalassemia, thalassemia major is considered the most severe.[2]

The prevalence of Beta-thalassemia is considered to be one of the highest among autosomal recessive disorders worldwide including the Middle East. The prevalence of β-thal globally is about (1.5 %) [3], and (0.05 %) in Saudi Arabia.[4] looking at β-thal prevalence in Saudi Arabia, there is a noticeable variance by region. Highest rates were observed in the region of Jazan with (3.2 %) for β-thal trait and (0.06 %) for β-thal major. The second highest rate was reported in the Eastern region with (2.37 %) for β-thal trait and (0.04 %) for β-thal major.[5]

Beta thalassemia major (TM) patients are usually presented with complications that include anemia, jaundice, growth retardation, failure to develop secondary sexual characteristics, hypothyroidism, osteoporosis, poor musculature, hepatomegaly, splenomegaly, expansion of the bone marrow, and myocardiopathy. These complications are more common in blood transfused TM patients who don't receive chelation therapy.[1]

Treatment options include transfusion along with chelation or stem cells transplantation with the latter being the only curative method with a success rate greater than (80.0 %). However, due to its limited availability, transfusion along with chelation therapy becomes the common choice of management in most centers.[6] The standard iron chelation therapy is based on the usage of deferoxamine. Effectiveness of this modality of treatments depends primarily on compliance of the medication.[7] Deferiprone (Ferriprox) is another oral chelator, which was recently approved in many countries including the United States.[8] The most common post-therapeutic complication due to iron chelation is liver fibrosis.[9]

Regularly observed complications include endocrine abnormalities with iron toxicity as the most likely cause of these complications in Thalassemia Major (TM) patients. Delayed puberty and hypogonadism are the most common endocrine complications of iron overload.[8]

The largest study of prevalence of endocrine complications was conducted in 2004, including 3,817 patients with TM in 29 countries. Of the patients, (36.0 %) were over 16 years. In addition, compliance with chelation therapy was poor in (51.0 %) of the patients. Results showed that hypogonadism was the most common complication in thalassemic patients with a prevalence of (40.1 %). The second most common complication was short stature presented in (31.1 %) of males and (30.5 %) of females. In addition, Abnormalities in glucose handling were relatively common in TM patients. The prevalence of Diabetes Mellitus (DM) in TM patients was (3.2 %). The frequency of hypothyroidism in patients with TM has been reported to be (3.2 %) followed by hypoparathyroidism (6.9 %).[10]

Lastly, several studies have suggested the lack of awareness about receiving chelating therapy especially among patients' parents, and for that reason, the awareness must be increased for a better outcome from the chelation therapy.[11] Blood transfusion in Beta thalassemia patients is mandatory to overcome and eliminate anemia, but iron overload that follows the transfusion process is the primary cause for the endocrine and metabolic complications. These complications are frequently faced by TM patients, and for this reason chelation therapy is a necessity. Despite the existence of several studies that aim to provide better understanding of the prevalence of endocrine and metabolic complications, very few highlighted the efficiency of chelating agents in reducing these complications and the influence of different factors that affect patients' intake and compliance to the chelation.

The first study, which took place in Tabriz, Iran, was investigating the metabolic and endocrine complications among Beta-thalassemia major patients older than 10 years (July 2008). The study investigated demographic data, medical, surgical and family history of patients presented with endocrine complications along with medications used. Menstruation history was also collected for female subjects

from the medical records of 56 patients who have been receiving blood transfusion for 13.16±4.65 years along with desferrioxamine. Other parameters such as luteinizing hormone, follicular stimulating hormone, height, fasting plasma glucose, oral glucose tolerance, thyroid stimulating hormone, free thyroxin and fasting calcium were obtained for all patients included in the study. Serum testosterone for males and serum estradiol for females were also studied. To monitor the effect of chelating therapy on the level of body iron, serum ferritin levels were measured.[12]

The study revealed that Hypogonadism was the most common endocrine abnormality as it occurred in (71.0 %) of TM patients. For females, hypogonadism was diagnosed by the presence of amenorrhea, whereas in males, hypogonadism was considered by the absence of testicular enlargement. Low serum testosterone levels in beta Thalassemia male adults were also observed. The second most common abnormality was short stature (51.8 %) and it was evident by growth failure with a height for age standard deviation score of less than –2. Moreover, short stature was found even in children who receive blood transfusion. Normal stature is thus rarely attained even in well-managed patients. Fasting blood glucose level and oral glucose tolerance tests were used to assess presence of diabetes mellitus by referring to American Diabetes Association and World Health Organization guidelines for the diagnosis of diabetes. The study revealed that the prevalence of impaired fasting glucose was (28.6 %), impaired glucose tolerance was (7.1 %) and diabetes was (8.9 %). The risk factors for diabetes in beta thalassemia patients include age, increased amount of blood transfusion, serum ferritin level, compliance with iron chelating therapy, family history of diabetes, and pubertal status. Overt primary hypothyroidism was present in (16.0 %) of patients (mean age, 17.33±4.22 years). Also, Subclinical hypothyroidism was observed in (10.7 %) of the patients. Hypoparathyroidism is a rare complication that is usually; but not always; accompanied by hypocalcemia (16.6 %). However, hypoparathyroidism may cause various neurological manifestations.[12]

The second study was conducted in 2004 by seven Italian centers and aimed to assess survival and complications in patients with TM treated with transfusion and deferoxamine. About 1073 patients were selected, 501 of whom were females and 527 were males. Of the 1073 patients, 977 were able to survive beyond the first decade of life (91.0 %). One hundred and fifty-seven patients (14.6 %) developed at least one complication.[13]

The results revealed that there was a significant association between birth cohort and complication-free survival *(p<.0005).* Survival and complication-free survival of patients with thalassemia major continue to improve, especially for female patients born shortly before or after the availability of iron chelation.[13]

The relationship between ferritin and hypogonadism in a subgroup 296 patients was assessed and 94 of them were found to have hypogonadism. Lower ferritin levels were marginally associated with a lower probability of hypogonadism (log scale, hazard ratio 1.31, *p=.059).* Ferritin level did not appear to be a significant lead predictor to hypothyroidism and diabetes mellitus.[13]

More than half of the patients in the multicenter Italian study had a delayed pubertal maturation. All of them, being born after 1970 or after started chelation therapy at the age of 10 or earlier. There was no

difference in frequency of pubertal maturation with increasing year of birth in the cohort born in 1970-1975. Diabetes, however, was reported as the cause of death in 7 patients. Survival and complication-free survival of patients with thalassemia major were found to improve especially for the patients born shortly before or after the availability of iron chelation.[13]

The third study assessed the reasons behind patients missing iron chelation therapy with desferrioxamine. A survey was forwarded to 10 countries: Cyprus, Egypt, Greece, Hong Kong, India, Iran, Italy, Jordan, Taiwan, and the United States. Three hundred questionnaires were sent to each country between October 1999 and January 2000, whereas 200 were sent to Greece. There were 1,888 replies (65.0 %) out of 2,900 questionnaires sent. Only 1,573 of the participants (54.0 %) used desferrioxamine. Patients' reasons for not being on chelator agents were divided according to: (1) access to drug, (2) adverse effects, (3) patient's feelings about the treatment, (4) inadequate support to continue with the treatment and (5) other reasons not listed on the questionnaire. Access to the drug was the most common issue in India (51.0 %, n = 26) and a frequent concern in Iran (25.0 %, n = 15), but in all other countries, it was a reason for less than (17.0 %) of patients. The most frequently reported category in those countries was related to their beliefs about the treatment (58.0 %, n = 387). The second most frequent reason was the adverse effects of infusing desferrioxamine (42.0 %, n = 277).[14]

Although the prevalence of complications related to blood transfusion in TM patients were studied in Saudi Arabia, to the best of our knowledge, there was no study to evaluate the prevalence of endocrine and metabolic complications in specific. Previous studies conducted in Eastern province did not highlight the difference of occurrence of such complications in blood transfused TM patients who receive chelating agent and those who do not receive it. In addition, barriers, or reasons for not being on such treatment were not assessed in previous studies conducted in the region.

Research Aim:

1. To evaluate endocrine complications that might occur in beta thalassemia patients.

2. To compare the onset of endocrine complications among patients who are compliant with chelation therapy and those who are not.

3. To assess the barriers that hinder compliance with chelating therapy.

Materials And Methods

- **Type of study:** This study is cross-sectional
- **Study population:** Saudi patients aged 2-30 years and of either sex diagnosed with beta-thalassemia who have received a blood transfusion and have been followed up in public hospitals or medical centers in the Eastern Province of Saudi Arabia.
- **Data sources:**

Haematology Units in public hospitals and medical centres in The Eastern Province of Saudi Arabia, including:

1. Qatif Central Hospital
2. King Fahad University Hospital in Khobar
3. Hereditary blood disease center in Al-Ahsa'a
4. Maternity and children hospital in Dammam

- **Inclusion criteria:**

Not establishing any of the above with the study population and exclusion criteria is sufficient to have the general characteristics of this study population.

- **Exclusion criteria:**

1. Patients with no medical history or no update within one year.

2. Pediatric patients who are not accompanied by their parents.

- **Sample size**:

A convenient sample of 89 patients were included in the study.

- **Study instrument**:

The tool which was used to collect the data is a semi-structured questionnaire. It is written in English and Arabic and it contains three sections. The questionnaires were filled by face-to-face interviews with the patients or their care givers. The First section of the questionnaire includes socio-demographic data of the child. The second section is composed of six questions to explore the history of the disease and the management received. The second section include both open and close ended questions. Close ended questions include yes/no and multiple choices with open-ended options in some of them. Endocrine abnormalities were assessed by evaluating the growth parameters, hormonal level and other laboratory data, which are included in the 3rd section of the questionnaire. Growth parameters consist of the weight, height, BMI for age and Z-score. Laboratory investigation results which were retrieved from the electronic files include the level of: Fasting blood glucose, Ferritin, serum thyroxine 3 and 4, thyroid stimulating hormone and parathyroid Hormone. For participants aged 16 and above: females were asked about their menstrual history and testosterone level was retrieved from medical records for males to assess gonadal complications. Results were considered normal or abnormal according to the World Health Organization and other international laboratory reference ranges attached in the appendix. Evidence for growth failure includes the assessment of height, body mass index for participants aged above 5 years and weight- height ratio for participants less than 5 years of age. All of which considered to be abnormal in the event of standard deviation less than -2. (Appendix 4-10) In addition, evidence for diabetes mellitus was based on American diabetes association and World Health Organization criteria.

Glucose tolerance was classified into 3 categories based on the fasting blood glucose: (1) fasting blood glucose < 5.5 mmol/l was considered normal; (2) fasting blood glucose of 5.5-7 mmol/l was defined as impaired fasting glucose; and (3) a fasting blood glucose ≥ 7 mmol/l warranted the diagnosis of diabetes. (Appendix 11)

Evidence for the existence of primary hypothyroidism was considered when free thyroxine was less than normal ≤ 0.8 ng/dl and thyroid-stimulating hormone was greater than normal ≥ 4 mIU/l. evidence for subclinical hypothyroidism was when free thyroxine normal 0.8-1.8 ng/dl and thyroid stimulating hormone was greater than normal ≥ 4 mIU/l. (Appendix 12,13)

- **Ethical consideration:**

The research proposal was approved by the research committee of the Arabian Gulf University. Also, an approval from the Saudi ministry of health and the assigned hospitals were obtained.

Prior to data collection, a verbal and written consent were obtained from the participants, we introduced ourselves as medical students and gave the patient an overview about the research topic and aim. Participants were informed that participation is voluntary, refusal to participate will not affect the treatment or involve any penalties, and the information will be confidential.

- **Statistical analysis:**

The data was entered and analyzed Using SPSS software version 23. Frequencies and percentages were computed for categorical variables. Mean and standard deviation were computed for quantitative variables. Cross-tabulation was done between two categorical variables. Simple bar chart and pie chart were plotted to present a categorical variable. Chi-Square test was used to determine whether there is a significant association between two categorical variables. *P-value = .05* was statistically considered significant.

Results

The clinical data of 89 patients (43 male and 46 females) with thalassemia major was obtained from four hospitals in the Eastern province of Saudi Arabia. Most participants were from hereditary disease center in Al-Ahsa'a, accounting for (44.9 %) of total study population. Participants ranged in age from 2 to 30 years. The mean age for participants was 15.5 years [σ ± 8.3; CI 95 %: 13.7 - 17.2] out of which 20 males and 21 females were above 16 years of age. The majority of participants were between the age of 11 to 20 years (37.1 %). (table 1)

Table 1: Demographical characteristics of patients with Beta Thalassemia major in Eastern Province of Saudi Arabia		
		n (%)
Hospital	Qatif central hospital	32 (36 %)
	Materinity and child hospital	8 (9 %)
	Hereditary diseases in Al-Ahsa'a	40 (44.9 %)
	King Fahad university hospital	9 (10.1 %)
	Total	89 (100 %)
Living area	Qatif	14 (15.7 %)
	Dammam	18 (20.2 %)
	Khobar	8 (9 %)
	Jubail	2 (2.2 %)
	Al-Ahsa'a	39 (43.8 %)
	Others	8 (9 %)
	Total	89 (100 %)
Gender	Male	43 (48.3 %)
	Female	46 (51.7 %)
	Total	89 (100 %)
Gender (Patient Age>16 years)	Male	20 (48.8 %)
	Female	21 (51.2 %)
	Total	41 (100 %)
Age in years	≤10 years	29 (32.6 %)
	11-20 years	33 (37.1 %)
	>20 years	27 (30.3 %)
	Total	89 (100 %)

Most of the participants were diagnosed before the first year of life with mean age of 1.91 years [σ ± 2.50; CI 95 %: 1.34 - 2.48] with minimum of 0 year and maximum of 13 years and have started blood transfusion around the same age of diagnosis (mean age 2.12 years) [σ ± 2.72; CI 95 %: 1.49 - 2.76]. Sixty four percent receive blood transfusion once every month. (table 2)

Table 2: Blood transfusion and chelation therapy in the study population		
		n (%)
Age at diagnosis in years	<1	35 (46.1 %)
	1 – 2	24 (31.6 %)
	>2	17 (22.4 %)
	Total	76 (100 %)
Receiving blood transfusion	Yes	86 (96.6 %)
	No	3 (3.4 %)
	Total	89 (100 %)
Age at starting blood transfusion in years	<1	34 (46.6 %)
	1 - 2	20 (27.4 %)
	>2	19 (26 %)
	Total	73 (100 %)
Number of times of receiving blood transfusion	Not every month	1 (1.2 %)
	Once a month	55 (64 %)
	Twice a month	27 (31.4 %)
	Three times a month	3 (3.5 %)
	Total	86 (100%)

Information obtained from interviews with patients, or their caregivers showed that (69.3 %) of participants were compliant to chelating agents while (21.6 %) were taking it but were not compliant.

Regarding receiving chelating agents, (21.6 %) of the study population were not compliant on taking chelating agents. At the same time (9.1 %) of the same study population were not taking chelating agents at all. The main reason for being non-compliant to chelating agents was the fact that it must be taken daily early in the morning on an empty stomach lifelong. On the other hand, the second most common reason was fearing the side effects which include nausea and vomiting.

Endocrine and metabolic complications were assessed in the study with the most prevalent abnormalities being underweight (40.9 %) followed by short stature (35.2 %). Primary hypothyroidism was observed in (17.0 %) of participants with mean age 24.00 years [σ ± 7.43; CI 95 %: 18.29 - 29.71] and subclinical hypothyroidism was present in (37.7 %) and lastly, diabetes mellitus was observed in (13.6 %) of participants with mean age 19.56 years [σ ± 5.92; CI 95 %: 15.01 - 24.10]. (table 3)

Table 3: Prevalence of endocrinopathies and menstrual abnormalities in Beta Thalassemia major patients in Eastern Province of Saudi Arabia		
Disorder		n (%)
Having menses for female > 16 years	Yes	14 (70 %)
	No	6 (30 %)
	Total	20 (100 %)
Hypothyroidism	Clinical	9 (17 %)
	Subclinical	20 (37.7 %)
	Normal	24 (45.3 %)
	Total	53 (100 %)
Diabetes	Diabetic	9 (13.6 %)
	Pre-Diabetic	15 (22.7 %)
	Normal	42 (63.6 %)
	Total	66 (100 %)
Height	Normal	57 (64.8 %)
	Short stature	31 (35.2 %)
	Total	88 (100 %)
BMI	Underweight	36 (40.9 %)
	Normal	47 (53.4 %)
	Overweight	5 (5.7 %)
	Total	88 (100 %)

Results of fasting blood glucose, serum T4, serum thyroid stimulating hormone (TSH), serum parathyroid (PTH) and testosterone were retrieved from the patients' folders after interviewing the patients or their care givers at the time of data collection and results showed that (25.8 %) of participants had impaired levels of glucose while (10.6 %) had high levels. Moreover, (3.8 %) had T4 levels lower than normal with (46.3 %) of participants having high levels of TSH. Testosterone level for males aged 16 years or above showed that (36.4 %) of them had low levels. Differences between the diagnosed cases and obtained serum levels could be explained by either the effect of receiving medications or failure to diagnose the cases early. Not all participants were featured in this table due to missing Laboratory data from the participants records at the time of collection. (table 4)

Table 4: Hormonal and biochemical tests related to endocrine disorders in beta thalassemia major in eastern province of Saudi Arabia

Test	Results	n (%)
Level of fasting blood glucose	Normal	42 (63.6 %)
	Impaired	17 (25.8 %)
	High	7 (10.6 %)
	Total	66 (100 %)
Serum level of T4	Low	2 (3.8 %)
	Normal	47 (88.7 %)
	High	4 (7.5 %)
	Total	53 (100 %)
Serum level of Thyroid stimulating hormone (TSH)	Normal	29 (53.7 %)
	High	25 (46.3 %)
	Total	54 (100 %)
Serum level of parathyroid hormone (PTH)	Low	2 (4.4 %)
	Normal	37 (82.2 %)
	High	6 (13.3 %)
	Total	45 (100 %)
Serum level of testosterone.	Low	4 (36.4 %)
	Normal	7 (63.6 %)
	Total	11 (100 %)

Relationship between receiving chelating agents and endocrine disorders among Beta Thalassemia major patients in Eastern Province of Saudi Arabia was studied and showed that patients who are compliant to chelation therapy had statistically significant lower prevalence of short stature *(P value= .05)* . and hypothyroidism *(P value= .05)*. On the contrary, BMI *(P value < .289)* and diabetes *(P value < .521)* Were poorly correlated to compliance with chelation therapy. (Table 5)

Table 5: Relationship between receiving chelating agents and endocrine disorders among Beta Thalassemia major patients in Eastern Province of Saudi Arabia

Disorder		Receiving chelating agents			P-value
		Yes	No	Yes, but non-compliant	
		n (%)	n (%)	n (%)	
Height	Normal	45 (75 %)	4 (50 %)	7 (36.8 %)	**0.007**
	Short stature	15 (25 %)	4 (50 %)	12 (63.2 %)	
BMI	Underweight	22 (36.7 %)	3 (37.5 %)	11 (57.9 %)	0.289
	Normal	35 (58.3 %)	5 (62.5 %)	6 (31.6 %)	
	Overweight	3 (5 %)	0 (0)	2 (10.5 %)	
Diabetes	Diabetic	4 (8.7 %)	1 (25 %)	4 (25 %)	0.521
	Pre-Diabetic	11 (23.9%)	1 (25 %)	3 (18.8 %)	
	Normal	31 (67.4 %)	2 (50 %)	9 (56.3 %)	
Hypothyroidism	Clinical	5 (15.2 %)	3 (60 %)	1 (6.7 %)	**0.024**
	Subclinical	11 (33.3 %)	0 (0)	9 (60 %)	
	Normal	17 (51.5 %)	2 (40 %)	5 (33.3 %)	

Discussion

This study aims to evaluate endocrine complications that might occur in beta thalassemia patients and the relation between receiving chelation therapy and the onset of these complications. The sample consisted of 89 patients, 2-30 years of age, attending hospitals in the Eastern Province of Saudi Arabia in 2019-2020. Endocrinopathies are common among beta thalassemia major patients as was reported by several studies [15-17]. Chelation therapy has a major role in decreasing or delaying such complications. Findings of this study might help in improving the quality of healthcare services provided to these patients by exploring barriers that hinder the compliance on chelating therapy.

Underweight was observed in (40.9 %) of our population compared to another study in Tehran where the prevalence of underweight participants reached (64.2 %).[18] Participants were considered underweight according to The Growth Charts for Saudi Children and Adolescents endorsed by The Health Services Council of Saudi Arabia, where a BMI less than -2 standard deviation was identified as underweight.

Subclinical hypothyroidism, which occurred in approximately (37.7 %) of our patients, was the most common endocrine abnormality. The prevalence of other endocrinopathies was: (35.2 %) short stature, (17.0 %) Primary hypothyroidism with mean age 24.00 years [σ ± 7.43; CI 95 %: 18.29 - 29.71], and (13.6 %) diabetes mellitus with mean age 19.56 years [σ ± 5.92; CI 95 %: 15.01 - 24.10].

The second most common endocrine dysfunction in this study was short stature (35.2 %), which is lower compared to a data from a study done across 16 countries and reported that (53.0 %) were short.[19] However, it is higher than that reported from a study of endocrinopathies in beta-thalassemia major in Northwest Saudi Arabia which was identified in (20.9 %) of their cohort.[17]

In our study (17.0 %) of the participants were found to have primary hypothyroidism which is higher than what was reported in other studies conducted in Tehran[15], Italy[16] and Northwest Saudi Arabia[17] ranging between (0-10.8 %). This difference in prevalence from other countries could be explained by the difference in cut-off hormone levels and/or variation in management protocols and patients' compliance between different centers. Prevalence of Hypothyroidism in the study was based on participants diagnosed with hypothyroidism and participants who met the diagnostic criteria at the time of data collection.

The rate of diabetes mellitus in this study was (13.6 %) where it has been reported to be (8.9 %) in a study conducted in Tabriz, Iran.[12] This has been suggested due to risk factors of diabetes including age, increased amount of blood transfusion, serum ferritin level, compliance with iron chelating therapy, family history of diabetes and pubertal status. Prevalence of diabetes in the study was calculated based on those who had high levels of glucose at time of data collection and those who were already diagnosed with DM.

There were no other studies conducted, to our knowledge, comparing receiving chelation therapy and onset of complications. There was a statistically significant association between those who are compliant to iron chelation therapy and the prevalence of some endocrine complications. Those who are compliant on chelation therapy had lower prevalence of short stature *(P value= .05)* and hypothyroidism *(P value= .05).* On the contrary, there was no significant difference in BMI *(P value < .289)* and diabetes *(P value < .521).*

In regard to receiving chelating agents most of the patients knew the importance of chelation therapy, but (21.6 %) of the study population were not compliant. There are several reasons for refusal of taking chelation therapy or not being compliant. The patients gave several reasons that we did not include them in our questionnaire (59.1 %) for not being compliant to chelation therapy. One of these reasons was that chelation therapy is a lifelong medication that must be taken daily on an empty stomach which is difficult

to be incorporate in their daily life routine. The second most common reason was fearing the side effects which include nausea and vomiting (31.8 %), and (9.0 %) thought it was not important nor available.

When compared with a study that assessed the reasons behind patients missing chelation therapy in several countries including, Iran, India and United States.[14] It has been shown that access to the drug was the main concern in India (51.0 %) which was also a common response in Iran (25.0 %) which was not the major cause in our study.

In other countries, however, the most common reason for non-compliance was related to their beliefs in taking the treatment (58.0 %). The second most common reason was the side effects of the treatment (42.0 %).

Conclusion

Despite the role of chelation therapy in the management of iron overload, the risk of secondary endocrine and metabolic complications remained considerable. Subclinical hypothyroidism and short stature were the most frequent endocrine complications encountered in this study. Hypothyroidism, Hypoparathyroidism, Diabetes mellitus and hypogonadism were also detected. Evaluating patients with TM should be carried out at early age and regularly. Patients Education regarding importance of compliance on chelation therapy since it has a role in decreasing several iron overload related endocrine and metabolic complications is essential.

Recommendations

Endocrinopathies and metabolic complications are common in Beta Thalassemia major patients receiving blood transfusion. Chelation therapy has a role in preventing or delaying such complications. Further longitudinal studies with a bigger sample size are needed to assess such complications and evaluate the role of chelation therapy. Proper protocols and guidelines should be developed and implemented by a multidisciplinary team with the emphasis of endocrine and metabolic complications screening to improve quality of care provided to this group of patients.

Limitations

There are few limitations to be considered in relation to the findings of our study.

First, the initial estimate of the sample size was 200, and we aimed to conduct a random sampling. However, the duration of data collection was limited to the summer in which most of the patients were away or traveling, hence they were not within easy reach. For that reason, we had a convenient sample of 89 patients.

Secondly, we could not attain the approval from hospitals easily, for instance one of the hospitals that was included in our protocol has not given the chance for data collection at all, making the sample size

smaller, therefore the statistical analysis remains of limited power.

In addition to that, the cohort is young which must have had an influence on the prevalence of age-related complications such as diabetes.

Another point to consider is the fact that, many of the laboratory tests required to assess endocrinopathies were not conducted or documented in some of the centers which made the assessment of complications challenging.

Declarations

Ethics Approval and Consent to Participate: The research and ethical committee, Arabian Gulf University approved the research. A signed written consent was obtained from all participants above the age of 18 and from the caregivers of participants who are below 18.

Consent for Publication: The authors affirm that the participants provided informed consent for publication.

Availability of Data and Materials: A semi-structured questionnaire was used to collect demographic data, medical histories. The questionnaires were filled by face-to-face interviews with the patients, or their care givers and the required laboratory data was retrieved from the medical records of patients attending hematology clinics across four different centers in Eastern province, Saudi Arabia.

Competing Interests: Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Figures

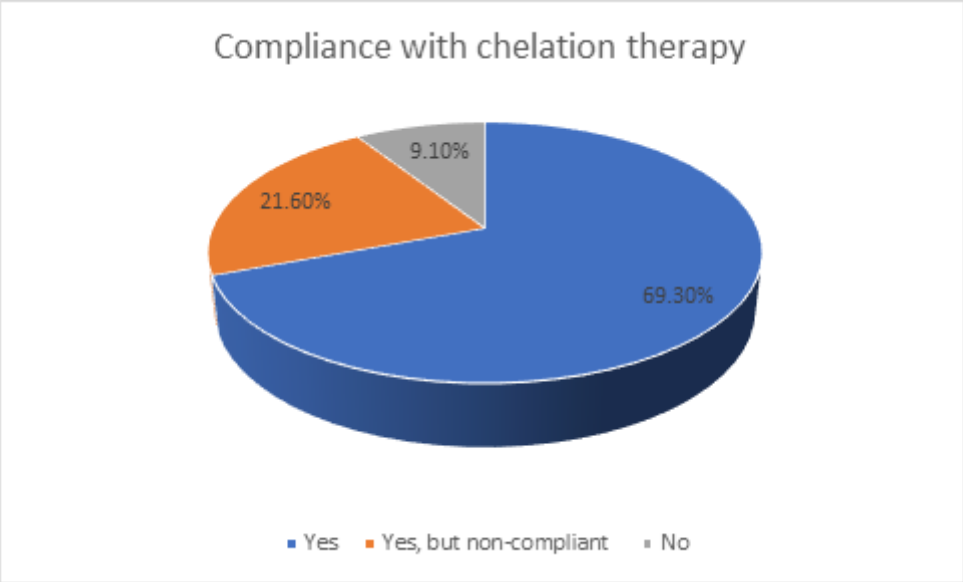

Figure 1

Compliance with iron chelation therapy among beta thalassemia major patients in the Eastern province of Saudi Arabia.

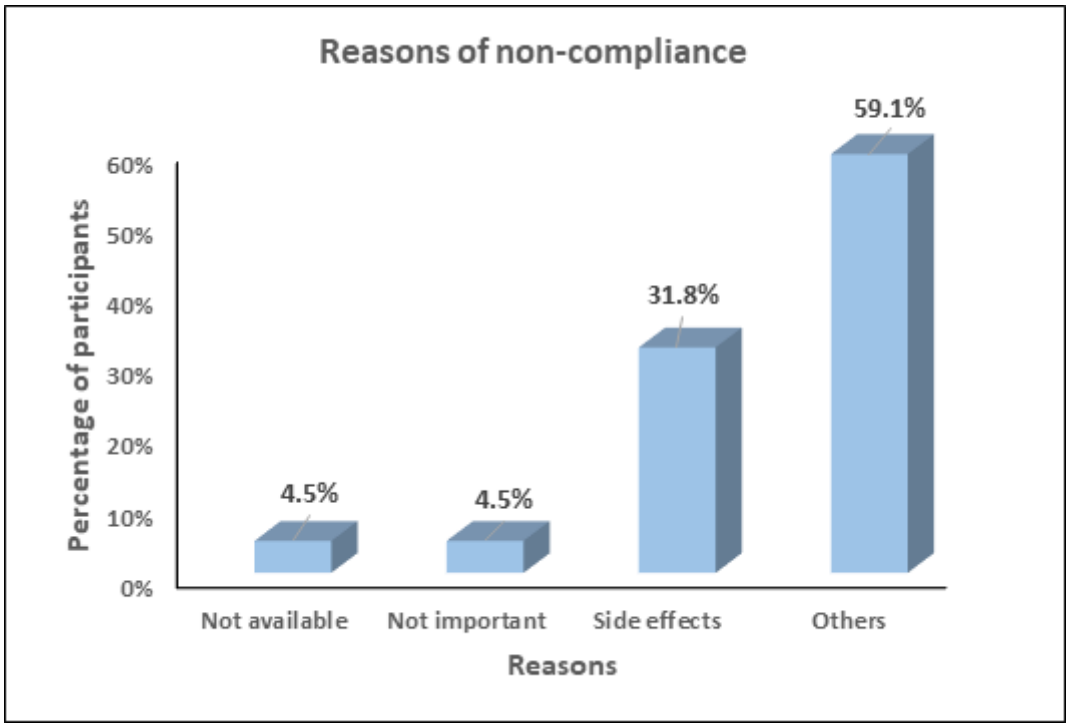

Figure 2

Reasons of not taking or non-compliance to chelating agents in the study population.

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