Assessment of Thyroid Function in patients with β- Thalassaimia Major and Intermedia: A comparative Study

Jamila Abdulsalam Abdulla (MBChB)[1] **and Ranan Kardagh Polus** (MBChB ,FICMS)[2]

Abstract

Background: Thalassemia is regarded as one of the most common hereditary disorders throughout the world. Endocrine disorders found among the commonest complications in thalassemic patients resulting from iron overload, especially thyroid.

Objective: To investigate thyroid function and complications in patients with Beta thalassemia major and intermedia in Erbil city.

Patients and Methods: This is prospective, cross sectional study (comparative study), the study was extended from September of 2018 till October of 2019 on 71 beta thalassemia major and 49 intermedia patients. The study was performed in the thalassemia center in Erbil city. Assay of thyroid hormones (thyroid function test) was performed by Roche Cobas E411 analyzer is fully automated immunoassay analyzer. Data were analyzed by using the statistical package for social science (SPSS) version22.

Results: This retrospective cross sectional study was carried out on 196 subjects, from which 71 patients with thalasseamia major ,49 patients with thalassemia intermedia, and 78 case were control subject.in the thalassemia major 8 cases (11.3) % had hypothyroidism (TSH high and low T4) and 17 case (23.9) % were subclinical hypothyroidism (TSH high and T3 AND T4 normal), in intermedia group about 13 patients had subclinical hypothyroidism, in compared to control group about 3 (3.9) % subclinical. In both TI and TMthy, the proportion of hypothyroidism and subclinical hypothyroidism was significantly (P=0.037) higher in those 18 years old (38.9%) compared to the lower age group (20.8%).

Conclusion: The thyroid function did not differ significantly by the other characteristics of the patients such as gender, consanguinity, chelation therapy, splenectomy status, organomegllay, BMI. Serum ferritin was found to be positively, but non-significantly correlated with T3 (r=0.78, p=0.398), negatively and significant statistically correlated with T4 (r=-0.231, p=0.011) and positively and significant statistically correlated with TSH (r=253, p=0.005).

Keywords: Hypothyroidism, Subclinical Hypothyroidism, Fhyroid function**.**

Corresponding Author: Jamilakurdistan@gmail.com

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[1]Rizgary Teaching Hospital- Erbil-Iraq.

[2]College of Medicine- Hawler Medical University-Erbil-Iraq.

Introduction

Thalassemia is regarded as one of the most common hereditary disorders throughout the world. The survival rate and consequent complications, depends on iron overload and toxicity on numerous body organs including endocrine glands which is caused by lifelong blood transfusion [1]. Beta-thalassemia syndromes are collections of inherited blood disorders most commonly as recessive traits, characterized by decreased or absent of β-globin chain synthesis due to mutation of globin gene, which results in reduced hemoglobin level in red blood cells, diminished RBC product and anemia. Three main groups have been categorized as thalassemia major, intermedia and minor [2,3]. Thalassemia minor is result if one of beta hemoglobin genes is affected. While, mutation of both beta hemoglobin genes will lead to either thalassemia intermedia or major, depending on the severity of the affected gene, clinically the thalassemia major is blood transfusion dependent while the intermedia is not[4.5].

Thalassaemia is the most common hemoglobinopathies in Iraq which 6_10% of the population have it. (6) latest study between university student in Erbil students have informed carrier rate of 7.8%[7] .There is in effective arthropisis.in sever beta-thalasseamia. the trademark of thalassaemia, which result of damaging effects of comparative excess of alpha chains. There is intramedullary decease of red cell precursor and enhanced intramedullary apoptosis of late erythroblast[8]. Transfusion in patient with thalassemia depends type of mutation present, for example thalassemia major may be essential in infancy at the begging of second month of life, in less severe cases, transfusion may not be required till the second year of life, but not often later[9].

Thyroid hormones are essential for regulation of metabolism every cell in body. The normal thyroid gland produces about 20% T3and 80% T4 however, T3 possesses about four times the hormone "strength" as T4. Regulation of thyroid hormones be influenced by pituitary gland When the level of thyroid hormones (T3 & T4) descent too low, the pituitary gland harvests Thyroid Stimulating Hormone (TSH)which excites the thyroid gland to produce more hormones, finally the thyroid gland secret more T3 and T4 Under the effect of TSH, thereby raising their blood levels [10]. Hypothyroidism is consequence of decrease production of thyroid hormone either depends on body demand or failing on receptor .in some recent study there is association between serum ferritin levels and hypothyroidism have been reported but in another there is no such correlation. Contrarily to major iron deposition in thyroid gland, short activity remains about subclinical hypothyroidism. [9].

Endocrine disorders found among the commonest complications in thalassemic patients resulting from iron overload, especially thyroid. The clinical consequences of excess iron deposition in thyroid gland demonstrated impaired thyroid (includes primary hypothyroidism-caused by abnormalities of thyroid, subclinical

hypothyroidism as well as secondary hypothyroidism) and parathyroid functions [11,12]. In 13_60% of patient with thalassaemia, Thyroid dysfunction has been informed and most frequently after 10 years of age [13]. Central hypothyroidism is infrequent. Histologically, installation of iron in the follicular epithelium and iron-laden macrophages of the interstitium (low or inappropriately normal" TSH and low free T4(.14) a normal serum T4 with a somewhat raised TSH level is defined Subclinical hypothyroidism. It is arguable whether patients with subclinical hypothyroidism should be managed[6].

This study aims to investigate thyroid function and complications in patients with Beta thalassemia major and intermedia in Erbil city. To evaluate the effect of iron overload on thyroid function through assessing (TSH, T3 and T4) in male and female patients. To find out prevalence rate(frequency) of thyroid dysfunction among thalassaemia major and intermedia. Up to researcher knowledge this study has not been in Kurdistan, because there is no sufficient information about thyroid function between thalassemia patient (major and intermedia).

Patients and Methods

The study was performed in the thalassemia center in Erbil city. This is prospective, cross sectional study (comparative study), the study was extended from September of 2018 till October of 2019, data collection was conducted through 4 months, from1st of August till 1st of December 2018. About 196 case were included in our study.49 cases were thalassemia major,71 cases thalassemia major and reminds were control, which is age and gender matched enrolled into the study after finding verbal permission from their legal keepers or patients.

The data collected included. General question like name, age, gender, consanguinity, religion, address of patient. Blood group.

History include, age at diagnosis, age of first transfusion, no of transfusion in unit, frequency of transfusion per week, history of splenectomy, age of splenectomy, history and type of chelation, viral screen especially viral hepatitis, also some clinical examination was done, height and weight, examination for splenomegaly and hepatomegaly.

Laboratory investigation

From each patient about 5 cc blood venous blood sample was withdrawn, sample were centrifuged and sera were separated and stored in _20 c for the thyroid hormones. Assay of thyroid hormones (thyroid function test) was performed by Roche Cobas E411 analyzer is fully automated immunoassay analyzer, made in Germany used broadly for diagnostic purpose. Using commercial kit (T3, T4, TSH,). Thyroid function was assessed by T3, T4, TSH hormones. Reference values T3 1.3_3.1 nmol/L,,,,,T4 66_181 nmol/L.

TSH 0.27_4.2 MU/ml (Roche Cobas E411 analyzer, made in Germany).

Serum ferritin was measured by Integra 400 plus fully automated immunoassay analyzer, made in Germany used broadly for diagnostic purpose. Using commercial kit

(FERR KIT). Reference value men:30_400 ng/ml,,,,, Women :15_150 ng/ml. Hemoglobin was measured by using sysmex automated hematology analyzer XT_2000 I which was made in Kobe, Japan. Electronic blood analyzer that was coulter counter was done in Rizgary hospital. Reference value Male 13_18 g/dl, Females 11.5_16.5 gm/dl.

That hypothyroidism is a graded phenomenon. The following grades have been identified. sub-clinical hypothyroidism has been reported: (normal T4, TSH 5-10 micro/ml). and1.

1-Primary Overt hypothyroidism is a combination of high TSH with low FT4, T3(15,16,17).

2-Central hypothyroidism(secondary) (low free T4, T3 and a low or inappropriately normal" TSH (14).

3-Sub-clinical hypothyroidism is a combination of high TSH with normal FT4 levels and T3 [15,16].

Ethical consideration

The study was approved by graduate Research Ethics Committee of college of Medicine of Hawler University.

Statistical analysis

Data were analyzed by using the statistical package for social science (SPSS) version22. Frequencies and percentages were used to present and summarize the categoricalvariable.chi_square test of association was used to compare proportions p value of ≤ 0.05 was considered statistically significant.

Results

This retrospective cross sectional study was carried out on 196 subjects, from which 71 patients with thalasseamia major ,49 patients with thalassemia intermedia, and 78 case were control subject. In thalassemia intermedia 25 cases were males, 24 were females while in thalassemia major 27 case were males and 44 case were females, whereas in control group 25 and 51 cases were males and females respectively. The details of characteristics of present study are shown in Tables (1).

In both TI and TM, the proportion of hypothyroidism and subclinical hypothyroidism was significantly (P=0.037) higher in those 18 years old (38.9%) compared to the lower age group (20.8%). The thyroid function did not differ significantly by the other characteristics of the patients such as gender, consanguinity, chelation therapy, splenectomy status, organomegllay, BMI etc Table (2).

The biochemical result of comparison between patients and healthy controls are expresses in table3. The result of current study showed that there is no statistically difference between healthy individual and patients with thalassemia major and intermedia regarding T3 values. The data analysis indicated a statistically significant decrease ($p < 0.01$) in mean concentration of T4 in serum of patients with thalassemia major in comparison with thalassemia and normal healthy subjects., this value proves that (Mean±SD) for THS was significantly

higher in thal. major when compared to thalassemia (intermedia and control peoples).

Data analysis of comparison between different groups reveal that hypothyroidism in the thalassemia major was 11.8%, subclinical hypothyroidism in the intermedia, major and control were,13,17,3 respectively.in the control group about 2.6 % were hyperthyroidism and subclinical hyperthyroidism. normal thyroid function test was 37.5 % in the intermedia .64.9 % was in the major and finally 90% in the healthy control group show in Table (4).

Serum ferritin was found to be positively, but non-significantly correlated with T3 (r=0.78, p=0.398), negatively and significant statistically correlated with T4 (r=-0.231, p=0.011) and positively and significant statistically correlated with TSH (r=253, p=0.005). Number of transfusions was found to be positively, but non-significantly correlated with T3 (r=0.003, p=0.976), negatively and significant statistically correlated with T4 (r=-0.344, p<0.001) and positively, but non-significant correlated with TSH (r=0.123, p=0.182) Figure (1,2).

Table (1): Host information of thalassemia major, thalassemia intermedia and reference group

Characteristic	No.	Range	Mean±SD
Age year	196	2-63	33.038 ±16.99
Weight (kg)	120	11_70	44. 3±14.65
Height (cm)	120	45_184	146.8750±21.42
BMI	120	11.8_54.3	20.93±5.73
Age at diagnosis(year)	120	1_58	6.03±8.54
Age at transfusion(year)	120	0.0_58	4.983±8.01
Number of transfusion(unit)	106	1_720	179.298±162.70
Age at splenectomy(year)	85	0._50	9.65±10.44
Hb(g/dl)	120	6.4_12.50	9.28±1.23
MCV/FL	120	43.1_88.5	71.89±10.42
MCH/PG	120	15.3_32.5	25.30±4.40
MCHC gm/dl	120	31_39.7	34.70±1.74
RDWA/FL	120	10_34.6	18.42±6.27
WBC 10^9/l	120	4.1_52	12.72±9.56
Platelet10^9/l	120	103_1102	424.55±231.88
T3 nmol/L	196	.66_7.4	2.12±0.842
T4nmo/l	196	22_191	103.88±26.88
TSH/µu/ml	196	.00_16	3.22±2.45
Serum ferritin ng/ml	120	81.0_12600	2175.86±2527.39
Hbf%	89	1.10_98.7	61.52±31.06

Table (2): Thyroid function status according to the sample characteristics in thalassemia intermedia and major patients

Characteristic	Thyroid function groups				Statistical evaluation P value
	Hypothyroidism		Normal		
	No.	%	No.	%	
Gender					
Male	19	36.5%	33	63.5%	.316
Female	19	27.9%	49	72.1%	
Age group					
<18 yrs	10	20.8%	38	79.2%	.037
=>18 yrs	28	38.9%	44	61.1%	
Blood group					
O+	18	36.0%	32	64.0%	NA
O-	1	50.0%	1	50.0%	
A+	7	25.0%	21	75.0%	
A-	2	66.7%	1	33.3%	
AB	5	41.7%	7	58.3%	
AB-	0	0.0%	1	100.0%	
B+	5	21.7%	18	78.3%	
B-	0	0.0%	1	100.0%	
Consanguity					
Positive	26	32.9%	53	67.1%	.684
Negative	12	29.3%	29	70.7%	
Splenectomy					
Yes	13	28.9%	32	71.1%	.612
No	25	33.3%	50	66.7%	
Organomegllay					
No	2	28.6%	5	71.4%	.374
Splenomegaly	8	50.0%	8	50.0%	
Hepatomegaly	13	26.5%	36	73.5%	
Hepatosplenomegaly	15	31.3%	33	68.8%	

Type of chelation					
	15	28.3%	38	71.7%	.671
Single	20	35.7%	36	64.3%	
Combined	3	27.3%	8	72.7%	
Viral screening					
Positive	19	48.7%	20	51.3%	0.924
Negative	17	21.5%	62	78.5%	
BMI					
Under Wt	11	28.9%	27	71.1%	.790
Normal	22	34.4%	42	65.6%	
Over Wt/Obese	5	27.8%	13	72.2%	
Chelation 2 Gr					
No	15	28.3%	38	71.7%	.481
Yes	23	34.3%	44	65.7%	

Table (3): Thyroid function test in comparison between patients with thal. major and intermedia and healthy control

Parameters	Thalassemia Intermedia patients (no=49)	Thalassemia Major patients (no=71)	Control groups (n0=76)	Statistical Evaluation P value
	Mean±SD	Mean±SD	Mean±SD	
T3 nmo/l	2.16±0.89	2.26±0.83	1.98±0.81	0.139
T4 nmo/l	110.30±19.04	92.85±25.80	110.05±29.O8	<0.001
TSH µu/ml	3.48±2.01	4.27±2.98	2.09±1.53	<0.001
Age (years)	23.18±12.31	19.69±8.96	44.11±15.70	<0.001

Table (4): Details of clinical thyroid function present in different group

Types	Thyroid function									
	Hypo		Subclinical Hypo		Normal		Subclinical Hyper		Hyper	
	No.	%	No.	%	No.	%	No.	%	No.	%
Thalassemia Intermedia	0	0.0%	13	26.5%	36	73.5%	0	0.0%	0	0.0%
Thalassemia Major	8	11.3%	17	23.9%	46	64.8%	0	0.0%	0	0.0%
Control	0	0.0%	3	3.9%	69	90.8%	2	2.6%	2	2.6%

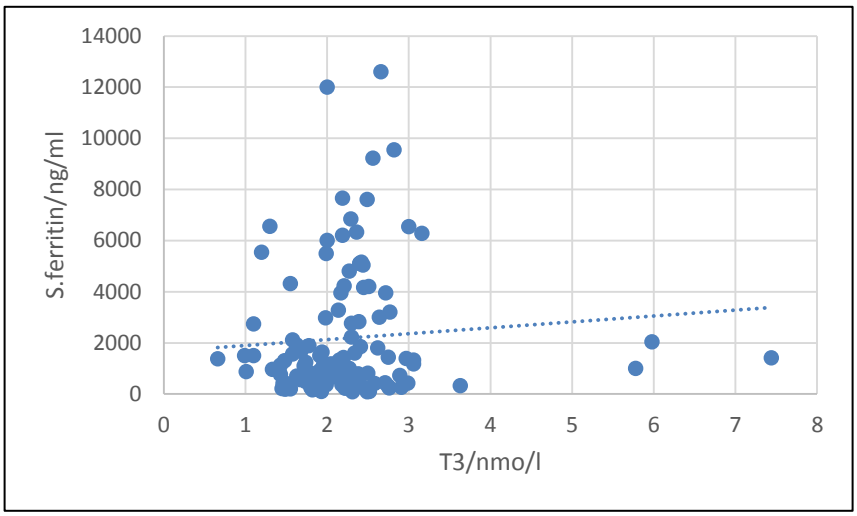

Figure (1): Correlation coefficient between serum ferritin and T3 in patient with thalassemia major and intermediar=0.078, P=0.398

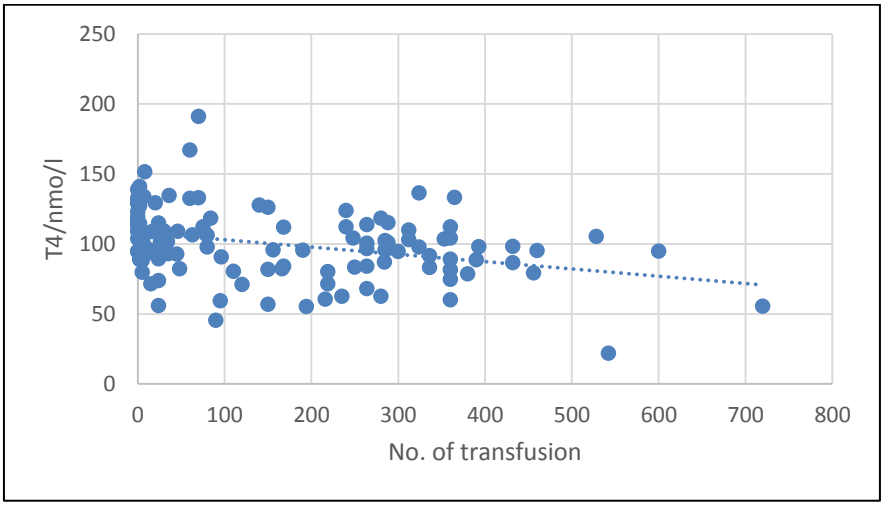

Figure (2): Correlation coefficient between mean number of transfusion and serum T4 level in patients with TI and TM patients together=-0.344, P<0.001

Discussion

The present study was carried out in Erbil, the Kurdistan Region of Iraq in order to examine their thyroid function and complications and the effect of iron overload on their thyroid function. The results of the study indicated that the studied patients aged 2 to 63 years with a mean age of 33.3years. Similar studies have reported almost similar age range for patients suffering from

thalassemia, particularly the minimum age. For example, in their study of patients with β-thalassemia intermedia in Northern Iraq, Al-Allawi et al. (2014) reported that the age range of the patients they studied was 2.5-49, which is similar to the result of the present study in terms of the patients' minimum age (18).

The results of the present investigation demonstrated that the prevalence of β-thalassemia major was higher in men than women, such that the male-to-female ratio was 1.62:1. This finding is almost in agreement with those of the study conducted by Mishra and Tiwari (2013) who reported a male-to-female ratio of 1.32:1 (19)This finding is also in line with the results of the study carried out by Hammod et al. (2018) who reported that thalassemia is more prevalent among males with 65% than females with 40%(20) However, as revealed by the results of the present study, prevalence rate of thalassemia intermedia among the studied patients was almost the same with 24 females and 25 males (the male-to-female ratio was 1.04:1). A similar result was reported by Al-Allawi et al. (2014) who showed that out of 74 patients with thalassemia intermedia, 36 were males and 38 were females with a male-to-female ratio of 1.05[1].

The results of biochemical test indicated that the three studied groups (patients with thalassemia major, thalassemia intermedia, and healthy individuals) were not significantly different in terms of their triiodothyronine (T3). However, the three groups were significantly different regarding their thyroxine (T4), and thyroid stimulating hormones (TSH) at a p-value of <0.0001. This finding was in good agreement with those of the study carried out by Asad et al. (2016) in Ahwaz, Iran [21]. Karim et al. (2016) also reported the similar results [22]. It was also observed that the patients with thalassemia (both major and intermedia) were significantly younger than the individuals in the control group ($p<0.001$). This finding can be justified by referring to the report that thalassemia usually afflicts infants and young children[23].

The results of the present study also demonstrated that hypothyroidism was more prevalent among the patients with thalassemia major and intermedia than the control individuals. This finding is in line with the results of the studies carried out by Eshragi et al. (2011) and Dolai et al. (2016) who referred to the prevalence of hypothyroidism in patients with thalassemia [24,25]. Moreover, the results showed that the three studied groups were significantly different in terms of their thyroid function at a p-value of <0.001, such that 26.5% of the patients with thalassemia intermedia and 35.2% of those with thalassemia major had hypothyroidism or subclinical hypothyroidism, while only 4.2% individuals in the control group had these thyroid dysfunctions. This finding is in line with the conclusions reported in previous studies indicating that prevalence of hypothyroidism is higher in patients with thalassemia than healthy individuals [26,27].

Finally, the results of the current study revealed that thyroid function and serum ferritin, this finding is in line with the results of the study carried out by Soliman et al. (2017) [28]. Moreover, number of transfusion and thyroid hormones These findings are relatively in line with those of the studies that have been conducted previously [21,29,30].

Conclusions

The patients with β-thalassemia major and intermedia have a higher risk of developing hypothyroidism and The patients with thalassemia major and intermedia were significantly different with control individuals regarding their thyroid function. Development of hypothyroidism was not correlated with blood type, consanguinity, splenectomy, Organomegllay, type of chelation, positive and negative results of viral screening, BMI, chelation. Our recommendation in this study early detection and management of thyroid function for these group of thalassemia can decrease the risk of hypothyroidism.

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