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Original Article

Associated Factors of Thalassemia and Thyroid Status of Thalassemic Patients

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Abstract

Thyroid dysfunction in thalassemia leads to the production of insufficient thyroid hormone which is responsible for various complications. Therefore, this study aimed to investigate the thalassemia related variables and thyroid status in the thalassemic patients. Data were collected from 138 thalassemia patients by using the questionnaire formulated after a detailed review of formerly published relevant literature. Statistical analysis was performed by using SPSS (v20, Inc., Chicago). An alpha level of 0.05 or less was considered as significant at 95% confidence interval. Around 76.1% of the patients were Hb E β-thalassemia patients including β-thalassemia major patient, β-thalassemia trait and Hb E trait and others (12.3%, 5.8%, and 2.9% respectively). History of blood transfusion had in 92% of patients. About 88% of these transfused respondents got frequent blood transfusion for the last 6 months. Iron chelator was prescribed in 58% patients either deferasirox (28.3%) or deferiprone (29.7%). Patients had the mean serum ferritin and hemoglobin level of 1682.43 (±1752.61) ng/dl and 7.81(±1.52) g/dl respectively. We found a strong correlation of transfusion dependency, interval between blood transfusions, iron chelator using and serum ferritin control with the thyroid status. The study also revealed that non-transfusion dependent and iron chelator independent respondents were less likely to develop hypothyroidism ($\chi^2 = 9.81$; $p = 0.002$ and $\chi^2 = 8.424$; $p = 0.004$, respectively). Hypothyroidism was more common in respondents with frequent blood transfusion compared with that of others ($\chi^2 = 11.276$; $p = 0.003$) and in respondent with bad control of serum ferritin than the respondents with good control ($\chi^2 = 13.929$; $p < 0.001$). The present study explored various thalassemia related factors including transfusion dependency, interval between blood transfusions, iron chelator using and serum ferritin control with the thyroid status. Further study is required to support our findings.

Keywords: *Thyroid status, thalassemia, hypothyroidism.*

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INTRODUCTION

Thalassemia is the most common monogenic blood disorder in the world.[1] It represents a group of recessively inherited hemoglobin disorders characterized by deficient synthesis of hemoglobin chains.[2] About 330000 babies are estimated to born each year with clinically significant hemoglobin disorder, 60000-70000 with severe form of thalassemia. Nearly 80% of these births occur in developing countries. Annually over 9 million carriers become pregnant, among which 1.7 million pregnancies both partners are carrier. As a result, 1.33 million pregnancies are at risk for a thalassemia major condition. In Southeast Asian region about 23000 conceptions are annually affected with thalassemia.[3] Bangladesh lies in the world's thalassemia belt but the information on epidemiology, mortality, complication and treatment outcome of thalassemia is lacking. The only published report on the prevalence of thalassemia showed 4.1% β thalassemia trait and 6.1% Hb-E trait among school children in Bangladesh. According to this study annually 1040 baby with β thalassemia and 6443 babies with E-beta thalassemia are born in our country.[4]

During this prolonged life thalassemic patients are suffering from various complication mainly caused by iron overload. Iron overload, if not treated properly, can lead to the most common thyroid gland complications.[5] The commonest form of thyroid dysfunction found in thalassemia is primary hypothyroidism which leads to insufficient production of thyroid hormone.[6] Thyroid hormones, thyroxine (T4) and triiodothyronine (T3) are the key regulator of metabolism and development of different organs, particularly of bone and central nervous system. They also help the regulation of lipids and protein breakdown in muscle, increase absorption of carbohydrate from intestine and increase dissociation of oxygen from hemoglobin. The hormone, mainly T3, regulates virtually every anatomic and physiologic component of cardiovascular system and acts on liver, adipose tissue, skeletal muscle and pancreas, influence plasma gluose level, insulin sensitivity and carbohydrate metabolism.[7]

Patients with optimally treated thalassemia can now enjoy a near-normal life and lifestyle and experience regular

physical and emotional development from childhood to adulthood. Leading a normal life is an often-expressed priority for patients. This includes social integration, connecting and interacting with people and contributing to society, despite counter forces that the disease and its treatment bring, which can lead to isolation and in some society's stigmatization. Global public health efforts alongside advances in medical management surely translated into prolonged survival and lower morbidity in patients with thalassemia. Despite these favorable effects, the burden of regular therapy poses a negative impact on patients' health-related quality of life.[8]

MATERIALS AND METHODS

Study design and study population

This cross-sectional study was conducted to find out the thyroid status among the thalassemic patients between January 2019 and December 2019.The total participants were 138 thalassemic patients. All the participants willingly joined in this study providing written consent and the study protocol was permitted by the department of Epidemiology, National Institute of Preventive and Social Medicine (NIPSOM), Banghobandhu Sheikh Mojibur Rahman Medical University [NIPSOM/IRB/2019/111].

Design and formulation of questionnaire

The questionnaire was designed after a detailed review of formerly published relevant literature. In accordance with the study objectives, some novel questions were developed. The questionnaire consisted of three sections which cover adequate information regarding demographic and socio-economic information, thyroid status, and thalassemia related problems.

Data collection

Data were collected by face to face interview, observation and record review. Socio demographic information, history of diagnosis and blood transfusion, some physical symptoms related to thyroid disorder were collected by face to face interview in the presence of expert physician. Data about current medication was collected from prescription. Data of serum ferritin, TSH and hemoglobin were collected by reviewing medical report. Height and weight were measured by measuring tape calibrated in centimeter and carry manual weighing scale respectively. During interview, privacy of the respondents was maintained as far as possible. All data were collected in the presence of physicians and nurses. Hospital record files were also checked to clarify the collected data. The patient who were willing to participate and fulfilled the selection criteria were taken as samples. Patients from both male and female who were at least 8 years of old were included in the study. However, mentally disabled and severely ill patients were excluded from the study.

Inclusion and exclusion criteria

Patients with thalassemia having thyroid problems were included in the present study. The patient who were willing to participate and fulfilled the selection criteria were taken as samples. Patients from both male and female who were at least 8 years of old were included in the study. However, mentally disabled and severely ill patients were excluded from the study.

Statistical analysis

All data obtained were entered into a Microsoft Office Excel 2010 spreadsheet and exported for analysis using SPSS software version 20.0 (SPSS Inc., Chicago, IL., USA). The p values were calculated by chi-square test. An alpha level of 0.05 or less was considered as significant at 95% confidence interval.

RESULTS

Socio-demographic profile

Table I depicts the socio-demographic profile of all volunteers. Mean age of all participants was 20.98 (±9.09) years and age range was 8 - 58 years. Here 6.5% respondents were at or below 10 years, 44.9% between 11and 18 years and rest were 19 years or above; where 51.4% of the participated patients were male and the rest were female. In religion Muslims was 94.2% and the rest 5.8% was Hindus. Among the respondents pre-primary level of education was found in 18.1%, 31.2% had completed primary level, 22.5% secondary level, 10% respondents had completed higher secondary of education. More than 10.1% higher secondary level, 6.5% post-graduation, 8.7% can sign only and 3.1% were illiterate or others. Among the respondents 47.1% were students. The rest were service holder (11.6%), businessman (6.5%), unemployed (19.6%) and 15.2% was housewife. In case of marital status, 73.2% was unmarried and 26.8% of the respondents was married. Among the respondents 94.9% had no history of consanguineous marriage of parents and others 5.1% had positive history of such marriages.

Table- I: Socio-demographic profile of thalassemic patients

Variables	Options	Thalassemic patients	
		Number (N = 138)	Percentage (%)
Age (Years)	≤10	9	6.5
	11 to 18	62	44.9
	≥19	67	48.6
Sex	Male	71	51.4
	Female	67	48.6
Religion	Muslim	130	94.2
	Hindu	8	5.8
Education (N = 108)	Pre-primary	25	18.1
	Primary completed	13	31.2
	Secondary completed	31	22.5
	Higher secondary completed	14	10.1
	Graduated/post graduated	9	6.5
	Sign only	12	8.7
	Illiterate & others	4	3.1
Occupation	Student	65	47.1
	Service holder	16	11.6
	Businessman	9	6.5
	Unemployed	27	19.6
	Others	21	15.2
Marital status	Married	37	26.8
	unmarried	101	73.2
Consanguineous marriage	Present	7	5.1
	Absent	131	94.9

Thalassemia related factors

Table II demonstrates the variables related to the thalassemia; here 76.1% of the patients were Hb E β-thalassemia patients including β-thalassemia major, β-thalassemia trait, Hb E trait and others (12.3%, 5.8%, 2.9% and 2.9%, respectively). Among them 73.2% were diagnosed at or before 10 years of age and rest were diagnosed after 10 years. The mean age of first blood transfusion was 9.18(±8.41) year and history of blood transfusion was recorded from 92% of patients. Among the transfused respondents 89% of them got frequent blood transfusion for the last 6 months (> 4weeks interval). Others got less frequent transfusion where interval between 2 successive blood transfusions was more than 4 weeks. Iron chelator was prescribed in 58% patients either deferasirox (28.3%) or deferiprone (29.7%). Among the 138 respondents, 72 were transfusion dependent and the rest 66 were non-transfusion dependent. Thyroid status was divided into euthyroid and hypothyroid; where 79.7% of the patients had the euthyroid condition of the thyroid function. The mean body mass index (BMI) of the respondent was 19.68 (±4.08) kg/m² and 44.2% were underweight, 46.4% normal, 5.8% respondents were overweight, 3.6% were obese. The lowest BMI was 13.02 and highest BMI was 33.78 kg/m. Patients had the mean serum ferritin level 1682.43 (±1752.61) ng/dl. The highest ferritin was 8318 ng/dl and lowest was 8 ng/dl.The mean hemoglobin of the respondent was 7.81(±1.52) g/dl ranged from 4.1 g/dl and maximum level was 11.9 g/dl.

Table- II: Distribution of thalassemia related factors.

Variables	Options	Thalassemic patients	
		Number (N = 138)	Percentage (%)
Type of thalassemia	β-Thalassemia major	17	12.3
	β-thalassemia trait	8	5.8
	Hb E β-thalassemia	105	76.1
	Hb E trait	4	2.9
	Others	4	2.9
Interval of transfusion (N = 127)	2-4 weeks	14	11
	> 4weeks	113	89
Iron chelation	Deferasirox	39	28.3
	Deferiprone	41	29.7
	No	58	42
Transfusion dependency	Transfusion dependent	72	52.2
	Non-transfusion dependent	66	47.8
Body mass index (BMI)	Underweight	61	44.2
	Normal	64	46.4
	Overweight	8	5.8
	Obese	5	3.6
Thyroid status	Euthyroid	110	79.7
	Hypothyroid	28	20.3
Ferritin control	Good control	63	45.7
	Bad control	75	54.3
Serum ferritin (ng/ml)	Mean = 1682.43 (±1752.61) ng/dl'; Max = 8318 ng/dl and Max = 8 ng/dl		
Serum Hemoglobin (g/dl)	Mean + 7.81(±1.52) g/dl; Max = 11.9 g/dl and 4.1 g/dl		

Association of socio-demographic and thalassemia related factors with thyroid status

Table III represents the association of socio-demographic profile with the thyroid status; euthyroid and hypothyroid. The here no statistically significant linkage of the socio-demographic characteristics including age (p = 0.557), sex (p = 0.059), religion (p = 0.205), education status (p = 0.062) and occupation (p = 0.352) with thyroid status of thalassemia patients.

Table- III: Socio-demographic characteristics and thyroid status of the respondents

Character	Variety	Thyroid status Euthyroid n (%)	Test statistic Hypothyroid n (%)
Sex	Female	58(86.6)	9(13.4)
	Male	52(73.2)	19(26.8)
Age	≤10	7(77.8)	2(22.2)
	11-18	52(83.9)	10(16.1)
	≥19	51(76.1)	16(23.9)
Religion	Islam	105(80.8)	25(19.2)
	Hinduism	5(62.5)	3(37.5)
Education	Preprimary & Primary completed	59(86.8)	9(13.2)
	Secondary completed to graduation	41(75.9)	13(24.1)
	Others	10(62.5)	6(37.5)
Occupation	Students	55(84.6)	10(15.4)
	Businessman & service holder	18(72)	7(28)
	Unemployed & others	37(77.1)	11(22.9)

Table IV presents the relationship between thalassemia-related factors and thyroid status. Thyroid status was categorized into euthyroid and hypothyroid; among those whose diagnosis and initial blood transfusion occurred at ≤10 years, the rates were 79% and 22% respectively. In contrast, for those diagnosed after the age of 10, the rates of euthyroid and hypothyroid were 31% and 6% respectively. However, this difference was not statistically significant ($p > .05$). However, this study found a strong relationship between transfusion dependency, the interval between blood transfusions, the use of iron chelators, and serum ferritin management with thyroid status. The study showed that non-transfusion dependent respondents were less likely to develop hypothyroidism ($\chi^2 = 9.81$; $p = 0.002$). Additionally, respondents not using iron chelators were also less likely to develop hypothyroidism compared to those who did use iron chelators ($\chi^2 = 8.424$; $p = 0.004$). Hypothyroidism was found to be more prevalent among respondents who received frequent blood transfusions compared to those who received them less frequently ($\chi^2 = 11.276$; $p = 0.003$), and among respondents with poor serum ferritin control compared to those with good control ($\chi^2 = 13.929$; $p < 0.001$).

Table- IV: Association between the thalassemia related factors and thyroid status

Character	Variety	Thyroid status		χ^2	p-value
		Euthyroid n (%)	Hypothyroid n (%)		
Age at the time of diagnosis	Diagnosis at ≤ 10yrs	79	22	0.519	0.471
	Diagnosis after 10 yrs	31	6		
Age at the time of first blood transfusion	≤ 10	77	20	0.488	0.463
	After 10	22	8		
Interval between blood transfusions	Frequent	6	8	11.276	0.003
	Less frequent	93	20		
Use iron chelator	Yes	57	23	8.424	0.004
	No	53	5		
Transfusion dependency	Yes	50	22	9.81	0.002
	No	60	6		
Serum ferritin	Good control	59	4	13.929	< 0.001
	Bad control	51	24		
BMI	Underweight	48	13	0.346	0.862
	Normal	52	12		
	Overweight and obese	10	3		

DISCUSSION

Mean age of the respondents was 20.98 (±9.09) years ranged from 8-58 years. A previous study also recoded the mean age 26.01years with age range from 12 to 60 years[9]. Most of the respondents (94.2%) were Muslims and rests were Hindus. About half of the respondents (51.4%) were male. Another study conducted on thyroid function of thalassemia patients in Pakistan showed 67% male and 33% female[10]. A large number of the respondents were students. The rest were service holder, businessman, unemployed and housewife. Majority of the respondent had no history of consanguineous marriage between parents. A review on global consanguinity showed North Africa, much of West, Central, and South Asia 20 to over 50% of current marriages are consanguineous[11].

In this study more than three fourth of the respondents (76.1%) were Hb E β-thalassemia patient. β-thalassemia major patient was 12.3%, β-thalassemia trait 5.8%, Hb E trait 2.9% and others 2.9%. Other study conducted on thalassemia patients showed 23.33% patients were with Hb E β-thalassemia, 41.67% Hb E trait, 30% Hb E disease, 3.33% β-thalassemia trait[9]. HbE-b-Thalassemia is also reported as the commonest form of Thalassemia in previous studies conducted by Rahman et al. and Mohanty et al[12,13].

Around 73.2% of thalassemia were diagnosed at or before 10 years of age. Another study found that 85% were diagnosed at or before the age of 8 years[12]. About 88% patients got frequent blood transfusion for the last 6

months (2-4 weeks interval). However, Malik et al. reported this percentage as 100% in the Pakistani patients[10]. The present study explored that iron chelator was prescribed to 58% patients. More than half (52.17%) of the respondents were transfusion dependent. However, no studies were found to support our findings. The mean body mass index (BMI) of the respondent participated in the study was 19.68(±4.08) kg/m². But a previous work depicted the mean BMI of thalassemia patients was 23.2(±4.3)[14]. About one-fifth (20.3%) of the respondents were found hypothyroid on the basis of TSH level obtained from medical record in this study. Others (79.7%) found euthyroid. The Lahore study on β-thalassemia showed 25.7% patient was primary hypothyroid[10]. Besides, a study conducted on 130 thalassemia patients in Iran demonstrated excess TSH in thalassemia patients[15]. Another study in India conducted among 100 thalassemic patients showed 10% patients were hypothyroid[16].

A detailed retrospective cross-sectional study in Ferrara, Italy showed pre-transfusion hemoglobin was 9.3(±0.3) mg/dl in thalassemic patients. Respondents had the mean serum ferritin level 1682.43(±1752.61) ng/dl. The highest ferritin was 8318 ng/dl and lowest was 8 ng/dl. Other study in Ferrara showed mean serum ferritin 777.1(±595.3) ng/ml[16]. These patients were all long lived and regularly followed since childhood that might be the cause of difference in mean serum ferritin level.

We did not find any significance differences of thyroid status by gender and age group. Smiler outcomes were recorded in previous studies conducted in Pakistan and India[10,16]. However, opposite scenario was observed in another study carried out by Salim et al.[17]. In this study hypothyroidism was found more common in respondents who got frequent blood transfusion (57.1%) than those who got less frequent blood transfusion (17.7%). Other study in India showed no significant relation between TSH and transfusion frequency[18].

Hypothyroidism was more common among transfusion dependent respondents (30.6%) than non-transfusion dependent respondents (9.1%). Guideline for the management of non-transfusion dependen Thalassemia (NTDT) showed that endocinopathies are less common in non-transfusion dependent thalassemia. The present study revealed no statistically significant linkage of age, gender, religion, education status and occupation with thyroid status of thalassemia patients in Bangladesh. However, the strong correlation of transfusion dependency, interval between blood transfusions, iron chelator using and serum ferritin control was found in the present study. Similarly, other study in Lahore showed significant difference between hypothyroidism and serum ferritin[10].

The study had some limitations that must be addressed. The demographic and thalassemia related data were insufficient due to the shortage of time and the availably time of patients. If we collected data on a large number of variables, it would be fruitful to represent the better scenario of the thyroid status of the Bangladeshi thalassemic patients. It was also difficult to get all information from patients due to their unfavorable condition. Besides, the finding of the study couldn't be generalized for all thalassemia patient as conducted on few patients who had the 3 medical tests within last 3 months. Furthermore, hypothyroidism was diagnosed on the basis of TSH level only so primary or subclinical hypothyroidism couldn't be differentiated.

CONCLUSIONS

This study explored various thalassemia related factors including transfusion dependency, interval between blood transfusions, iron chelator using and serum ferritin control with the thyroid status. Non-transfusion dependent respondents and respondents who were not taking iron chelator were less likely to develop hypothyroidism. Hypothyroidism was found more common in respondents got frequent blood transfusion than those who got less frequent blood transfusion and in respondent with bad control of serum ferritin. Further study is required to support these findings.

Conflict of Interest

Authors have no conflict of interest and no fund was received from any sources.

Ethical Clearance

The study was approved by the department of Epidemiology, National Institute of Preventive and Social Medicine (NIPSOM), Banghobandhu Sheikh Mojibur Rahman Medical University [NIPSOM/IRB/2019/111]

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