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Endocrine and metabolic manifestations of thalassemia in Bangladeshi patients: A narrative review

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Abstract

Dysfunctions of the endocrine glands due to progressive iron deposition produces different hormone deficiencies in patients with transfusion-dependent thalassemia. With increasing life expectancy, managing complications including endocrine and metabolic complications is becoming important. In this review, we summarized the published original articles from Bangladesh highlighting the endocrine and metabolic complications of patients with thalassemia. In general, evidence is scarce without any reporting regarding glycemic, adrenal, and pituitary status. Endocrinologists should come forward with a team approach involving Hematologists and Transfusion Medicine Specialists to lead this research field further. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2023; 2 (1): 19-23]*

Keywords: Thalassemia; Bangladesh; Thyroid; Calcium; Lipid; Hypogonadism

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Introduction

Thalassemia is an autosomal recessive disorder that causes ineffective erythropoiesis with cumulative deposition of iron in different tissues (secondary hemochromatosis), causing progressive organ dysfunctions.[1] Currently, there is no curative treatment for thalassemia except hemopoietic stem cell transplantation (HSCT). However, HSCT requires high cost and technical expertise which is lacking in most developing countries. Besides, most patients lack suitable donors for HSCT. Therefore, regular blood transfusion and iron chelation are the mainstay of treatment for patients with thalassemia.[2] Inadequate chelation therapy leads to iron deposition in different organs. Endocrine glands are susceptible sites for iron deposition. Besides, the presence of dysfunctions of other organs and oxidative stress associated with iron deposition further affect the function of the hormone axes, making the management complex.[3]

Bangladesh is located in the world's thalassemia belt. However, a population-based prevalence study is lacking. A study conducted among 207 reproductive-aged women living in rural areas found a prevalence of about 28% of thalassemia (β-thalassemia and HbE disease).[4] Among 735 school children from six divisions of Bangladesh, the overall prevalence of the β-thalassemia trait was 4.1% and the hemoglobin E trait was 6.1%.[5] A hospital-based study on patients with thalassemia reported that the common type of disease was Hb-E-β-thalassemia (77.25% among 1594). Around 91% of patients required blood transfusion, of whom 73% were transfusion-dependent thalassemia (TDT).[6]

Several barriers are present in the prevention and management of thalassemia in Bangladesh. Consanguinity of marriage is common in patients with thalassemia (15%).[7] Inadequate healthcare infrastructure, poor knowledge about the disease, and limited resources are important issues.[6,8,9] Despite these negative influences, the life expectancy of people with thalassemia is increasing. The focus of management has now shifted to the quality of life. As a result, the management of complications is now a priority.[10]

Endocrine and metabolic complications of thalassemia include the involvement of all the glands with a preference for some. Common endocrine disorders include hypogonadism, hypothyroidism, and diabetes mellitus in patients with thalassemia major, especially TDT but poorly chelated patients.[10,11] Although less in frequent, around 50% of patients may suffer from short stature and growth hormone deficiency contributes to around 27% of cases.[12] Most of the data are derived from developed countries and there is a scarcity of data from developing countries. This review aimed to summarize the endocrine and metabolic complications

among patients with thalassemia in Bangladesh from published literature.

Methods

A literature search was carried out up to 30 November 2022 in the 'Research Gate', 'Banglajol', and 'PubMed' with the keywords 'Thalassemia' AND 'Bangladesh'. From Research Gate, among 71 articles, endocrine-related 8 articles were found. From 'Banglajol', among 72 articles 8 articles were relevant. Among 87 articles, endocrine-related 5 articles were found for review from PubMed. After removing three duplicate articles, 18 relevant original articles (endocrine and metabolic) were included in this review.

Results

The main findings are described below.

Hypogonadism

A study conducted in the Department of Transfusion Medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU) among 94 patients (age: 13 - 30 years, m/f: 50/44) with a transfusion frequency of approximately one unit/ month (β-thalassemia major: 80, severe HbE-β thalassemia: 14). They defined hypogonadism up to Tanner stage II and then defined its type by serum follicle stimulating hormone levels. Around 35% had hypogonadism (m/f: 36%/34% individually for each sex) comprising 18% of eugonadotropic, 12% hypogonadotropic, and 5% hypergonadotropic hypogonadism. Patients with hypogonadism had significantly higher levels of serum ferritin than those with eugonadism.[13]

Short stature

Among 175 children with short stature, only 2 had thalassemia (1.14%) in a study conducted in a Paediatric Endocrine OPD of a tertiary care hospital.[14] Among 100 patients with thalassemia syndrome (age ≤12 years), 57 had growth retardation reported from a Pediatrics Department of a medical college hospital.[15]

Thyroid function tests

Gosh and Chakrabarti showed that serum TSH and ferritin levels fall with chelation and maintain a linear relationship among 500 patients with thalassemia major with an age of more than 6 years.[16]

Among 54 patients with β-thalassemia major and 54 healthy individuals matched by sex and age (<12 years, m/f ratio equal in each group), there were no significant differences in thyroid function.[17]

In another study, hypothyroidism (overall: 30%) was present in 28.6% (total: 65) of the boys and 66.7% (total: 56) of girls with TDT.[18]

Percentages of subclinical hypothyroidism were significantly higher in 50 patients with TDT than in control (26.0% vs. 2.5%) without significant association with serum ferritin levels.[19]

Among 86 children (aged: 5 - 18 years, m/f: 51/35, received at least 10 times of blood transfusion) with thalassemia (β-thalassemia/ HbE-β-thalassemia: 21/65), 1 had primary hypothyroidism and 8 had subclinical hypothyroidism (10.5% jointly). Hypothyroid patients had higher status (≥2000 ng/dL) of serum ferritin than euthyroid patients.[20]

Bones and minerals

Sultana and Akhter carried out a study among 40 TDT and 20 age and sex-matched healthy control (5 – 25 years). The patients with thalassemia had lower levels of calcium (Ca: 6.9 ± 2.2 vs. 9.0 ± 0.5, mg/dL, mean ± SD) as well as higher percentages of hypocalcemia (<8.5 mg/dL) than the healthy control (67.5% vs. 32.5%). On the other hand, patients with thalassemia syndrome had higher levels of serum phosphate (iPO4: 6.0 ± 1.4 vs. 4.1 ± 1.4, mg/dL, mean ± SD) as well as higher percentages of hyperphosphatemia (>4.7 mg/dL) than the control group (85.0% vs. 15.0%).[21]

Urmi et al. published two articles among 35 male patients with TDT and an equal number of matched healthy control (15 - 40 years). They also showed lower levels of serum corrected Ca (8.9 ± 0.1 vs. 9.3 ± 0.1, mg/dL, mean ± SD) and intact parathormone (iPTH) (32.0 ± 1.3 vs. 39.1 ± 1.1, pg/mL, mean ± SD) and higher levels of serum iPO4 (4.2 ± 0.2 vs. 3.5 ± 0.1, mg/dL, mean ± SD) as well as alkaline phosphatase (103.3 ± 8.9 vs. 69.0 ± 2.1, U/L, mean ± SD) in those with TDT than in the controls. However, only one patient with TDT had primary hypoparathyroidism. While serum ferritin correlated with corrected Ca and iPO4 but not with iPTH in patients with TDT.[22,23]

Munira et al. reported two studies among 30 cases of TDT with iron chelator (5 – 40 years) and an equal number of matched controls. Patients with TDT had lower levels of serum total Ca (8.6 ± 0.1 vs. 9.1 ± 0.1, mg/dL, mean ± SD) and magnesium (Mg: 1.8 vs. 1.9, mg/dL, mean) but higher levels of serum ferritin (6276.9 ± 709.8 vs. 40.4, 7.7, µg/L, mean ± SD) than the control group. Around 6.7% and 13.3% of patients with TDT had hypocalcemia (<8.1 mg/dL) and hypomagnesemia (<1.6 mg/dL) respectively. A negative correlation was observed between serum ferritin with both serum Ca and Mg. Besides, 3.3% of TDT patients had hypozincemia (<0.55 mg/L) and 13.3% had hypercupremia. (>155 µ

g/dL).[24,25]

Significantly lower serum levels of Ca (7.9 ± 0.6 vs. 8.5 ± 1.1, mg/dL, mean ± SD, p<0.001), magnesium (1.88 ± 0.2 vs. 2.2 ± 0.32, mg/dL, mean ± SD, p=0.05), and insignificantly higher levels of iron, sodium, and potassium have been found in patients with β-thalassemia major in comparison to healthy individuals.[17]

Among 121 (m/f: 65/56) patients with TDT, the mean serum zinc (Zn) and copper (Cu) levels were lower than the lower limit of the standard value range but the Mg levels were within the range in both sexes. Low levels of Zn (<63.8 µg/dL) and low levels of Cu (m<70, f<80 µ g/dL) were present in 83.5% and 62.2% of cases respectively.[18]

Nandy et al. found similar levels of serum Cu between 30 patients with thalassemia major (5-15 years) and an equal number of healthy controls.26

Among 72 (aged: 6 – 39 years) patients with TDT, 15 (20.8%) patients had a low bone mineral density in the left femoral neck.[27]

Low body mass index (BMI)

Low BMI levels were observed among TDT patients than healthy controls.[22,24] Among 120 adults with thalassemia syndrome, only 1.67% had optimal BMI (18.5 - 23 kg/m^2) and 33.3% had a BMI <16 kg/m2.[28]

Lipid profile

Among 121 children with thalassemia, mean levels of all lipid fractions including high-density lipoprotein cholesterol (HDL-C) were lower than the lower limit of normal levels. High triglyceride (TG) (m ≥131, f ≥ 135, mg/dL), and low HDL-C (m <63.42, f <56.84, mg/dL), were present in 25.2% and 58.67% of patients respectively.[18]

Among 40 (age >12 years; m/f: 22/18) patients with β-thalassemia major, significantly lower HDL-C and low-density lipoprotein (LDL-C) were observed than controls p<0.001. But total cholesterol (TC) levels were statically similar among the study groups. Serum TG and LDL-C had positive but HDL-C had negative correlations with ferritin levels and amount of blood transfusion.[29]

Among 30 patients (5 - 15 years) with β-thalassemia major, significantly lower levels of HDL-C and LDL-C than controls were observed. However, serum TG levels of β-thalassemic patients were significantly higher than in control in both sexes. But TC level was statistically similar between the study groups.[30]

Discussion

An international multicenter study conducted among 3817 adolescents and adults with β-thalassemia major showed that lack of pubertal change (40.5%, m/f: 43%/38%) was the most common endocrinopathy.[31] Iron deposition in the pituitary is the main mechanism along with a less frequent contribution from the deposition in gonads.[32] Chowdhury et al. found a little bit lower prevalence of hypogonadism. Different prevalence is possible as it depends on several factors.[11]

The multicenter study also reported the prevalence of short stature in 31.1% of males and 30.5% of females.[32] However, Ali et al. reported short stature in 57% of children with thalassemia.[15] Not only growth hormone deficiency, malnutrition, and mineral abnormalities are important contributing factors for growth retardation.[10] Studies conducted among Bangladeshi patients with thalassemia also found lower levels of Ca, Mg, and Zn but higher levels of iPO4 and Cu in patients with thalassemia.[17,18,21-26] Hypoparathyroidism is a relatively uncommon complication, also observed by Urmi et al.[23] Low bone mass is an important thalassemia bone disease that is caused by several factors including growth hormone deficiency and hypogonadism.[33] Even among adequately treated adults, nearly 93% might present with low bone mass.[34] The low prevalence (~20%) of low bone mass reported by Biswas et al. might be the measurement of bone mineral density in the femoral neck only without reporting other sites.[27]

A systematic review and meta-analysis of cross-sectional studies showed a prevalence of 16.22% of hypothyroidism (subclinical and overt) in patients with TDT.[35] Studies conducted among Bangladeshi patients reported a wide range of prevalence of different levels of hypothyroidism (10.5% to 30%).[18-20] The positive correlation between TSH and ferritin, observed in these studies, is similar to the meta-analysis.[16,20,35]

Studies published from Bangladeshi patients reported lowers levels of LDL-C and HDL-C than in controls with contradictory findings for TC and TG.[18,29,30] A study published from Indian population found lower levels of TC and HDL-C but higher levels of TG among 100 children with β-thalassemia major than the control group.[36] A study reported from Iran also found lower TC but higher TG among patients with thalassemia major.[37] Hypocholesterolemia reflects excess consumption for RBC membrane formation and does not necessarily protect from atherosclerosis.[38]

Limitations

Most of the studies were done to evaluate the bones, mineral, and thyroid aspects of TDT patients. Other hormone levels were not adequately evaluated and adrenal and glycemic aspects were not reported at all.

Recommendations

In National guidelines on Thalassemia of Bangladesh, endocrine complications, as well as management are discussed, but endocrine referral was not suggested.[39] So, a team involving Endocrinologists, Hematologists, and Transfusion Medicine Specialists should come forward to explore the field of endocrine and metabolic complications in Bangladeshi patients with thalassemia.

Conclusions

There is a scarcity of data regarding the endocrine and metabolic complications of Bangladeshi patients with thalassemia. Current evidence suggests that a significant percentage of TDT patients are affected by endocrine and metabolic complications. A multidisciplinary team approach is required to manage and progress the research activities further.

Conflict Of Interest

The authors have no conflicts of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

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