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ORIGINAL ARTICLE

# Endocrinopathy in thalassemia major patients on chelation therapy: A study of North Indian population

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## ABSTRACT

**Background:** Beta-Thalassemia major is a hereditary disorder of haemoglobin resulting in severe anaemia. Despite advances in its treatment endocrine complications frequently cripple patients and affect their quality of life. We studied the relationship between endocrine dysfunctions in thalassemic patients as well as the effect of chelation therapy on endocrinopathy.

**Methods:** This is a descriptive–cross sectional study conducted between May 2014 and October 2014 on transfusion-dependent beta thalassemia major patients attending the thalassemia clinic of our hospital. Medical records of 100 patients above the age of 10 years were reviewed for endocrine status. Hormonal analysis had been done by fully automated immunoassay analyser based on technique of electro-chemiluminescence immunoassay (ECLIA).

**Results:** Hypothyroidism was present in 20% patients. Amongst the hypothyroid patients, 55% had overt deficiency while 45% had subclinical hypothyroidism. Hypogonadism was noted in 42% patients out of which 83.3% had hypogonadotrophic hypogonadism and 16.6% had normogonadotrophic hypogonadism. About 10% had both thyroid and gonadal dysfunction. A significant difference in mean serum ferritin was noticed in patients with or without endocrinopathies.

**Conclusion:** There is a high prevalence of endocrine complications amongst the thalassemic patients on chelation therapy. This observation signifies the importance of frequent follow-ups for early detection of complications.

**Key Words:** Thalassemia major, chelation therapy, thyroid dysfunction, gonadal dysfunction, Endocrinopathy, hemoglobinopathy

**Abbreviations:** **FSH -** Follicle Stimulating Hormone; **LH -** Leutinizing Hormone; **TSH -** Thyroid Stimulating Hormone; **fT3** – free Tri-iodo thyronine; **fT4** – Free tetra-iodo thyronine (Thyroxine )

## Introduction

Beta-thalassemia major represents a group of recessively inherited hemoglobin disorders. It was first described by Cooley and Lee.[1]The cornerstone in the management of thalassemia major is life-long blood transfusions to combat severe dyserythropoietic anaemia along with frequent iron chelation therapy to minimize the deleterious effect of chronic iron deposition in tissues.[2]

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The combination of early diagnosis and improvements in supportive therapy have improved the life expectancy of these patients[3], thus transforming thalassemia from being a fatal disease of childhood to a chronic disease compatible with adult life. Despite these advances patients are still prone for long-term endocrine complications which substantially affect their quality of life.

Abnormal thyroid function is a common finding in these patients. Chronic tissue hypoxia[4] and iron overload are thought to have direct toxic effect on the thyroid gland. High concentrations of labile plasma iron and labile cellular iron have been implicated in the formation of free radicals and production of reactive oxygen species. This may cause damage at the cellular and organ system level.[5]

Moreover, in severe iron overloaded thalassemia, secretion of regulatory hormonal such as FSH, LH and TSH may be disrupted due to anterior pituitary damage.[6] The commonest form of thyroid dysfunction seen in thalassemics is subclinical hypothyroidism. Its frequency is reported to be 6-30% in different countries depending upon chelation regimens used.[7] Although symptoms of thyroid dysfunction are non-specific, it affects all organ systems, thereby emphasizing the importance of early laboratory evaluation and control of thyroid function.

The present study was aimed to evaluate thyroid function, pituitary gonadotropin levels (FSH, LH) and gonadal function in patients with beta thalassemia major and to assess its relation, if any, with serum ferritin levels.

## Methods

This is a descriptive, cross-sectional study conducted during May 2014 to October 2014. Transfusion-dependent beta thalassemia major patients attending the Thalassemia Clinic of our hospital were included in the study. The study cohort consists of 100 patients above the age of 10 years.

The diagnosis of homozygous thalassemia was based on the characteristic haematological features in peripheral blood smear evaluation and hemoglobinopathy screening at presentation. Diagnoses made in childhood were also accepted. The study protocol was a naturalistic observation, an integral part of the routine clinical monitoring through reviewing of the medical records. The most recent values of the parameters fT3, fT4, TSH, FSH, LH, estradiol, testosterone and ferritin were considered for analysis. Hormone analysis was done in dedicated hormone lab using a fully automated immunoassay analyser (Cobas e411, Roche) based on the technique of electro-chemiluminescence immunoassay (ECLIA).

All the patients enrolled in this study had regular transfusion of packed red blood cells once in every 3-4 weeks ever since early years of life and all of them had received iron chelation therapy (Desferrioxamine 20-50 mg/ Kg daily).

Laboratory evidence for hypogonadism was based on finding low FSH and LH with low estradiol or testosterone (hypogonadotrophic hypogonadism), or normal FSH and LH with low estradiol or testosterone (normogonadotrophic hypogonadism). The thyroid function status of the patients was classified as subclinical hypothyroidism (TSH above reference range but below 10µUL/ml, normal fT4 and fT3 or overt disease (increased TSH, decreased fT4 and/or fT3) hypothyroidism primary or secondary hypothyroidism with low TSH and low fT4.

The data was analyzed using SPSS statistical software. The results were analyzed and numerical data presented as mean ± SD (standard deviation). The statistical difference in serum ferritin between two different groups of patients with or without endocrinopathies was assessed using unpaired student's test.[8] The statistical significance was assigned for $P<0.05$.

## RESULTS

Among the study subjects 62% were males and 38% were females, with a mean age of 14.0±2.1 years. Hypothyroidism was present in 20% (12 males, 8 females) patients. Amongst the hypothyroid patients, 55% (n=11; 7 males, 4 females) had overt hypothyroidism while 45% (n=9; 5 males, 4 females) patients had subclinical hypothyroidism. Hypogonadism was present in 42% (n=42; 27 males, 15 females) out of which 83.3% (n=35; 22 males, 13 females) had hypogonadotrophic hypogonadism and 16% (n=7; 5 males, 2 females) had

**Table 1: Hormonal profile of the study population.**

| Thyroid Function | | | | Gonadal function | | | |
|---|---|---|---|---|---|---|---|
| Hormones | Normal (n=48) | Subclinical HT (n= 11) | Overt HT (n=9) | Hormones | Normal (n=48) | NGT-HG (n=7) | HGT-HG (n=35) |
| fT4 (ng/dl) | 1.11 ± 0.57 | 1.1 ± 0.15 | 0.69 ± 0.06 | FSH (IU/l) | 5.57±2.11 | 3.26± 1.70 | 1.36 ± 1.16 |
| TSH (µIU/ml) | 2.43 ± 1.02 | 4.8 ± 0.27 | 5.54 ± 0.69 | LH (IU/l) | 4.97±2.17 | 2.04± 0.41 | 0.78±0.86 |
| | | | | Estradiol (pg/ml) | 54.79±10.61 | 13.2± 2.26 | 20.98±9.36 |
| | | | | Testosterone (ng/dl) | 468.89±156.47 | 158.8± 27.30 | 48.90± 66.32 |

NGT-HG - Normo Gonadotrophic Hypogonadism; HGT-HG - Hypo Gonadotrophic Hypogonadism 20 patients had both thyroid and gonadal dysfunction

normogonadotrophic hypogonadism. 10% of the thalassemia major patients had both thyroid and gonadal dysfunction while 48% had no endocrinal abnormality.

The mean ferritin levels of the thalassemia major patients with endocrine dysfunction and those without any endocrinal abnormality were 3330±1450 ng/ml and 2008±1234 ng/ml respectively ($p<0.0001$) indicating significant difference in the ferritin levels between two groups.

## DISCUSSION

Endocrine dysfunction is the second most frequent complication of beta thalassemia major. Over 60% of thalassemic patients after the age of 10 years are known to have dysfunction of at least one endocrinal gland and about 40% have multiple Endocrinopathies. [9] High prevalence of endocrinal disorders in these patients has been reported by several authors [10-13], who have attributed these abnormalities to iron overload. The histological studies of different endocrine glands have also supported this hypothesis.[14-15]

In the current report, hypogonadism was found to be the frequent endocrine disorder affecting 42% of the thalassemia major patients. About 83% had hypogonadotrophic hypogonadism while 16% had normogonadotrophic hypogonadism. Gonadotropin deficiency or gonadal failure is manifested in males by delayed or arrested puberty and in females by absence of menarche, discontinuation of regular menstruation or secondary amenorrhoea.[16]. The pituitary–gonadal axis has been reported to be highly sensitive to iron deposition leading to hypofunction of these glands, particularly in the form of secondary hypogonadism, which is rarely reversible with iron chelation therapy.[17] Thus prevention with early institution of chelation therapy is the standard care.

Other possible causes of hypogonadism in patients of beta–thalassemia major include liver disorders, chronic hypoxia, diabetes mellitus and zinc deficiency [18]. Hypogonadism is found in more than 40% of thalassemic patients [19], with pubertal delay in emergence of gonadal functions. Different studies report different prevalence rates of hypogonadism. While one study reports it to be 17% [10], another longitudinal study reports the prevalence to be 75% in girls and 62% in boys [20]. Hormone replacement therapy is recommended in these patients. However, the dosage should be balanced after taking into consideration the age of initiation and coexistence of other organ dysfunction particularly heart, liver and skeletal systems. [21]

The prevalence and severity of hypothyroidism vary in different cohorts. Some studies reported a high prevalence of primary hypothyroidism, reaching up to 17-18%, while a few others reported a low prevalence of 0-9% [22-23].In the present study, 20% of the thalassemia major patients had hypothyroidism, amongst which 55% had overt hypothyroidism and 45% had sub-clinical hypothyroidism. In a recent survey, high prevalence of primary overt hypothyroidism was present in 16% of the beta-thalassemic patients. [24] In studies with low prevalence of overt hypothyroidism, mild thyroid dysfunctions were more common as reported in 12% of patients. [25] Hypothyroidism occurs in a significant proportion of thalassemia major patients. Therefore regular follow-up for early detection and timely treatment can improve the quality of life of these patients.

Finally, there was a significant difference in mean ferritin levels in those with and without endocrinal dysfunction. These findings yield the importance of iron overload in development of endocrinopathies. There is contradiction between the different studies regarding the relation between ferritin levels and endocrinopathies. While some studies revealed a positive relationship [10,26-28], others did not. [25,29-30]. It has been suggested that the survival prognosis for the thalassemic patients is excellent with serum ferritin concentration is below 2500 μg/l. [3]

Further studies on larger population can be planned for detection and prevention of the endocrinal dysfunctions. Whether the development of complications amongst the patients is due to variations in the treatment protocol or differences in individual susceptibilities, requires more detailed study.

## CONCLUSION

High prevalence of endocrine complications amongst the thalassemic patients emphasizes the importance of therapeutic intervention, frequent follow-up and monitoring for early detection of complications and initiation of replacement therapy.

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