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Endocrine and Biochemical Dysregulation in Beta-Thalassemia: Pathophysiology and Biomarkers

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ABSTRACT

Objective: To evaluate the prevalence and pattern of endocrine dysfunctions in transfusion-dependent beta-thalassemia patients.

Methodology: A cross-sectional study was conducted on 34 transfusion-dependent beta-thalassemia patients (mean age 17.35±2 years) from Pakistan. Hormonal and metabolic profiling was performed using chemiluminescent immunoassay (CLIA), and serum ferritin levels were measured to assess iron overload.

Results: All patients exhibited severe iron overload (mean ferritin 12,617±4,959.63 ng/mL). The most common endocrinopathies were hypogonadism (67%), predominantly in males (52%), followed by hypothyroidism (19%) and hypocalcemia/vitamin D deficiency (87%), with 32.3% showing severe deficiency. Significant correlations were observed between LH and testosterone ($r=0.924$, $p<0.001$) and FSH and testosterone ($r=0.634$, $p=0.004$), indicating primary gonadal failure, along with an inverse relationship between fT4 and calcium ($r=-0.366$, $p=0.043$). Serum ferritin showed no significant correlation with endocrine parameters ($p>0.05$).

Conclusion: Endocrine dysfunctions are highly prevalent among transfusion-dependent beta-thalassemia patients and are influenced by multiple factors beyond iron overload. Routine endocrine screening should be integrated into thalassemia management for early detection and intervention.

Key Words: Thalassemia, Iron overload, Endocrinopathies.

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4,5]Critical analysis and manuscript review; [6,7]Data analysis; Manuscript Editing

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Introduction

Beta-thalassemia is one of the most prevalent autosomal recessive hematological disorders worldwide and represents the most common inherited hemoglobinopathy. It poses a significant public health burden, particularly in regions such as the Middle East, the Indian subcontinent, Africa, and Southeast Asia, where the carrier frequency is notably high. The highest prevalence rates have been reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia.[1] According to the Thalassemia International Federation (TIF), approximately 200,000 patients diagnosed with beta-thalassemia major are currently registered and undergoing regular treatment across the globe.[2]

In Pakistan, an estimated 5,000 to 9,000 children with beta-thalassemia are born annually, with an estimated carrier rate of 5-7%, translating to

approximately 9.8 million carriers within the total population.[3] Beta-thalassemia is classified into several clinical phenotypes, including beta-thalassemia trait (carrier state), beta-thalassemia intermedia, beta-thalassemia major, and beta-thalassemia compound heterozygotes. These variants exhibit a wide spectrum of clinical manifestations, ranging from asymptomatic microcytic anemia to severe transfusion-dependent anemia.[4] The disease results from mutations or deletions in the beta-globin gene, leading to a reduction ($beta^{+}$) or absence ($beta^{0}$) of beta-globin chain synthesis. This impaired synthesis causes an imbalance in globin chain production, resulting in an excess of unstable alpha-globin chains. These surplus alpha chains precipitate within erythroid precursors, causing premature destruction and abnormal erythroid maturation in the bone marrow.[5] The precipitation of alpha-globin chains forms intracellular inclusions, leading to oxidative membrane damage, mechanical injury to erythroid precursors, and ultimately ineffective erythropoiesis. Consequently, beta-thalassemia syndrome is characterized by significant intramedullary destruction of red cell precursors. Additionally, defective and rigid red blood cells undergo hemolysis within the splenic microcirculation, leading to progressive splenomegaly and exacerbation of anemia.[4]

The hallmark of beta-thalassemia is chronic anemia, which triggers compensatory erythropoietin production, stimulating extensive bone marrow expansion and proliferation. This compensatory mechanism often results in skeletal deformities, bone marrow hyperplasia, and excessive dietary iron absorption, leading to iron overload in vital organs.[6] The cornerstone of management for thalassemia major includes lifelong blood transfusions and iron chelation therapy to prevent hemosiderosis and associated complications.[7] However, regular transfusions significantly contribute to iron overload, as a single unit of whole blood contains approximately 200-250 mg of iron.[8] Without adequate chelation therapy, progressive iron accumulation leads to severe complications such as cardiomyopathy, hepatic fibrosis, and endocrinopathies. Jensen et al., reported that approximately 66% of transfusion-dependent beta-thalassemia patients develop a single endocrine disorder, while 40% present with multiple endocrinopathies. These include hypogonadism, hypothyroidism, growth hormone deficiencies, diabetes mellitus, hypoparathyroidism, and, rarely, adrenal insufficiency, particularly in older patients with elevated serum ferritin levels.[9,10]

Thyroid hormones play a crucial role in physical and intellectual development, and hypothyroidism is recognized as a risk factor for cardiovascular disease.[11] Moreover, osteoporosis and pathological fractures due to reduced bone mineral density are alarming consequences in iron-overloaded thalassemic patients. The prevalence of hypoparathyroidism in these patients is reported to be up to 4%.[12,13] Hypogonadism, the most common endocrine complication in beta-thalassemia patients (affecting 40-91%), significantly impacts their quality of life, leading to infertility and psychological distress.[14]

In order to assess the hormonal and biochemical changes in these patients due to the disease itself and regular transfusions, this study was designed to assess the prevalence and impact of endocrine abnormalities in multi-transfused beta-thalassemia patients, with a particular focus on hypogonadism, hypothyroidism, hypocalcemia, and vitamin D deficiency. Additionally, the study aims to evaluate the correlation between iron overload and endocrine dysfunction to enhance understanding of the long-term complications associated with beta-thalassemia.

Methodology

A cross-sectional descriptive study was conducted, enrolling thirty-five multi-transfused patients

diagnosed with beta-thalassemia syndrome and managed at Fatimid Foundation, Peshawar. Patients aged 15 years and above who had received more than 12 regular blood transfusions were included in the study after obtaining written informed consent from either the patients or their guardians.

A detailed medical history was recorded before conducting clinical examinations and blood sample collection. Blood samples were immediately transported to the Hematology Laboratory at the Institute of Basic Medical Sciences. Upon arrival, the samples were centrifuged at 4,000 revolutions per minute for 10 minutes. The serum was carefully separated and stored in labeled screw-cap Eppendorf tubes, coded with unique patient identifiers.

To ensure analytical precision, the laboratory procedures were initially performed using Liquichek Bio-Rad calibrators and controls at both low and high concentration levels. A calibration curve was generated using calibrator values within the established reference ranges. The quality control process involved comparing the obtained control values against standard quality control charts to monitor reagent performance and assay consistency. After quality assurance, serum samples were analyzed for follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol, thyroid-stimulating hormone (TSH), free thyroxine (fT4), triiodothyronine (T3), calcium, vitamin D, and ferritin levels using the Chemiluminescence Immunoassay (CLIA) technique. The tests were conducted using Acculite Monobind Diagnostic kits on a Lumax® analyzer from Monobind Incorporation, USA.Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics were applied, where categorical variables were expressed as frequencies and percentages, while continuous variables were reported as mean ± standard deviation (SD). Pearson's correlation test was utilized to examine associations between numerical variables, while the student's t-test was employed to compare means between two groups.

Ethical approval was taken from **Regional Blood Center Peshawar**, (No.M/RBC/Estt:/2022-23) on 09-03-2023 and from **Pak International Medical College, Department of Medical Research**, Peshawar. (PIMC/DMR/15)

Results

A total of 34 beta-thalassemia patients were included in this study, comprising 21 males (61.76%) and 13 females (38.24%). The age of the participants ranged from 15 to 24 years, with a mean age of 17.35 ± 2 years. All patients demonstrated significant iron overload, with serum ferritin levels ranging from 5,000 ng/mL to 27,042 ng/mL, and a mean ferritin value of 12,617 ± 4,959.63 ng/mL.

Endocrine Abnormalities: Endocrine abnormalities were highly prevalent among the study participants, with hypogonadism being the most common, identified in 67% of patients. This condition showed a notable gender disparity, affecting 52% of males and 15% of females, reflecting the greater susceptibility of male patients to gonadal dysfunction, possibly due to the differential impact of iron overload on the testes compared to the ovaries.

Hypothyroidism was documented in 19%, consistent with existing literature on thyroid dysfunction in transfusion-dependent thalassemia patients, likely attributable to iron deposition in the thyroid gland. Additionally, a significant majority (87%) of the patients presented with hypocalcemia and vitamin D deficiency, metabolic abnormalities that may predispose them to osteopenia, osteoporosis, and increased fracture risk. Among these, 32.3% had severe deficiencies, while 54.85% exhibited mild to moderate insufficiencies, underscoring the need for routine screening and early intervention to prevent long-term skeletal complications (Figure 1).

Correlation Analysis: Pearson correlation analysis

was performed between serum ferritin, calcium, vitamin D, thyroid profile (TSH, FT4), gonadotropins (FSH, LH), and sex hormones (testosterone, estradiol).

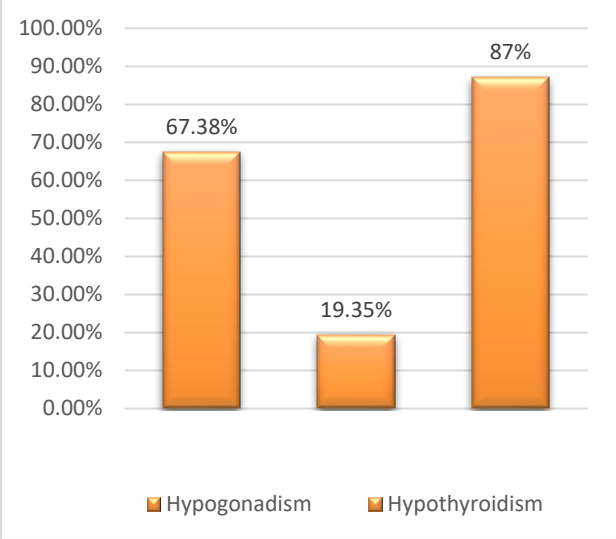

Figure 1: Frequencies of different endocrinopathies

Table I: Descriptive statistics of biochemical parameters

	Mean	Std. Deviation	N
Current S. Ferritin ng/ml	12258	4959.63	31
Vit D ng/dl	16.05	10.07	31
Serum Calcium mg/dl	8.39	1.05	31
S.TSH uIU/ml	2.73	2.06	31
S.FT4 ng/dl	1.32	.3010	31
S.FSH mIU/ml	6.62	5.63	31
S. LH mIU/ml	1.84	2.37	31
S. Testosterone ng/ml	1.63	3.04	19
S. Estradiol pg/ml	40.20	26.31	12

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

- A statistically significant negative correlation was observed between serum calcium and FT4 (r = -0.366, p = 0.043).
- FSH exhibited a significant positive correlation with both LH (r = 0.440, p = 0.013) and testosterone (r = 0.634, p = 0.004).
- LH also showed a strong positive correlation with testosterone (r = 0.924, p < 0.001).
- No significant correlations were detected between serum ferritin and other variables including vitamin D, FT3, TSH, FSH, LH, or testosterone (Table 2).

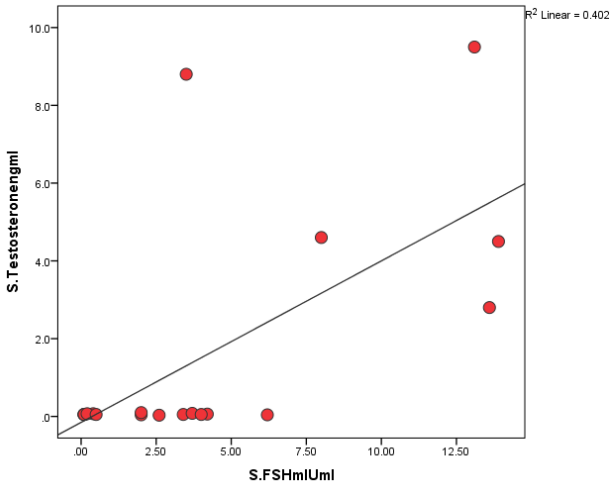

Figure 2: Scatter plot between FSH and Testosterone

A direct positive correlation was noted between serum FSH and testosterone levels, suggesting that as FSH increases, testosterone levels also tend to rise.

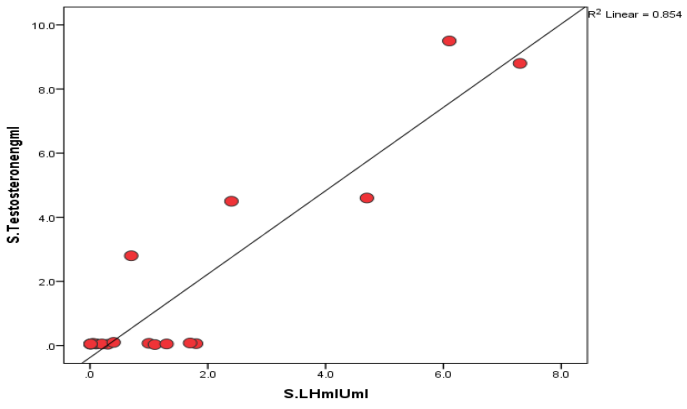

Figure 3: Scatter plot between LH and Testosterone

Table II: Pearson correlations between serum calcium, FT4, FSH, LH, and testosterone levels						
		S. Calcium Mgdl	S.FT4 Ngdl	S.FSH mIUml	S.LH mIUml	S.Testosteroneng ml
S. Calcium	Pearson Correlation	1	-.366*	.030	.085	-.058
	Sig. (2-tailed)		.043	.873	.649	.812
	N	31	31	31	31	19
S. FT4ngdl	Pearson Correlation	-.366*	1	.077	-.050	-.153
	Sig. (2-tailed)	.043		.682	.788	.533
	N	31	31	31	31	19
S. FSH mIUml	Pearson Correlation	.030	.077	1	.440*	.634**
	Sig. (2-tailed)	.873	.682		.013	.004
	N	31	31	31	31	19
S. LHml Uml	Pearson Correlation	.085	-.050	.440*	1	.924**
	Sig. (2-tailed)	.649	.788	.013		.000
	N	31	31	31	31	19
S. Testosteronen g/ml	Pearson Correlation	-.058	-.153	.634**	.924**	1
	Sig. (2-tailed)	.812	.533	.004	.000	
	N	19	19	19	19	19
*. Correlation is significant at the 0.05 level (2-tailed).						
**. Correlation is significant at the 0.01 level (2-tailed).						

A significant direct positive relationship was observed between serum LH and testosterone, indicating that higher LH levels are associated with increased testosterone levels.

Discussion

The study cohort predominantly consisted of young adults, with a mean age of 17.35 years, reflecting a typical demographic pattern observed in transfusion-dependent beta-thalassemia patients in Pakistan and other developing countries where early diagnosis and lifelong transfusion therapy are common. Consistent with the literature, all patients in this study demonstrated significant iron overload, as indicated by the markedly elevated serum ferritin levels (mean: 12,617 ng/mL). Endocrine dysfunction is a well-recognized complication of iron overload in beta-thalassemia due to iron deposition in endocrine glands, impairing their physiological function. Hypogonadism was the most prevalent endocrine abnormality in this study, affecting approximately 67.38% of the patients, with a higher prevalence among males. This finding aligns with existing studies reporting hypogonadism as the most frequent endocrinopathy. The strong positive correlations observed between gonadotropins (FSH and LH) and testosterone levels further support the diagnosis of primary hypogonadism in these patients, likely due to iron deposition in the testes and pituitary gland.

Hypothyroidism was observed in 19.35% of patients, corroborating previous findings indicating hypothyroidism prevalence rates ranging from 10-25% in transfusion-dependent beta-thalassemia populations. Although serum FT4 levels were within

the normal range on average, a significant inverse correlation was identified between FT4 and serum calcium, suggesting a potential link between thyroid dysfunction and calcium metabolism in this cohort.

A striking finding was the high prevalence (87%) of hypocalcemia and vitamin D deficiency, which reflects the susceptibility of thalassemia patients to bone metabolism disorders due to endocrine dysfunction, iron toxicity, and impaired vitamin D synthesis. Severe vitamin D and calcium deficiencies were observed in one-third of the patients, which may predispose them to osteoporosis, bone pain, and pathological fractures, common complications in beta-thalassemia major.

Interestingly, no significant correlation was found between serum ferritin and most endocrine parameters such as vitamin D, thyroid hormones, and gonadal hormones. This suggests that while iron overload is a contributing factor to endocrine dysfunction, other factors, including genetic predisposition, suboptimal chelation therapy, or chronic inflammation, may also play a role.

The positive associations found between FSH and testosterone, as well as between LH and testosterone, highlight an important compensatory mechanism wherein the hypothalamic-pituitary axis may respond to peripheral gonadal insufficiency by increasing gonadotropin secretion. However, despite elevated gonadotropins, testosterone levels remained low, suggesting primary testicular dysfunction.

Conclusion

This study confirms that multi-transfused beta-thalassemia patients are highly susceptible to endocrine complications, especially hypogonadism, hypothyroidism, and metabolic bone disease due to vitamin D and calcium deficiencies. The findings underscore the need for routine endocrine screening in thalassemia management protocols. Early identification and timely management of endocrinopathies can improve the quality of life and clinical outcomes for these patients.[15]

Limitations: A key limitation of this study is the relatively small sample size, which may affect the generalizability of the findings. Additionally, serum ferritin, although a widely used marker, may not fully capture total body iron burden due to its variability with inflammation and other factors. MRI imaging for hepatic and cardiac iron would have provided a more comprehensive assessment of iron overload.

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