

*To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
A Prospective Cohort Study*

**“TO STUDY ENDOCRINE MANIFESTATIONS IN CHILDREN
AND ADOLESCENTS WITH THALASSEMIA MAJOR
A PROSPECTIVE COHORT STUDY”**

BY

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Dissertation submitted to

B.L.D.E (DEEMED TO BE UNIVERSITY) VIJAYAPURA KARNATAKA



In partial fulfilment of the requirements for the degree of

DOCTOR IN MEDICINE IN PEDIATRICS

UNDER THE GUIDANCE OF

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B.L.D.E. (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL

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2024

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and genuine research work carried out by **Dr MANASI SALUNKHE** in partial
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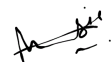
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ABBREVIATIONS

BMI - Body Mass Index
DBP - Diastolic Blood Pressure
FBS - Fasting Blood Sugar
FSH - Follicle Stimulating Hormone
Hb - Hemoglobin
HbA1c - Glycated Hemoglobin
LH - Luteinizing Hormone
PPBS - Post-Prandial Blood Sugar
PR - Pulse Rate
RBS - Random Blood Sugar
SBP - Systolic Blood Pressure
SD - Standard Deviation
T3 - Triiodothyronine
T4 - Thyroxine
TSH - Thyroid Stimulating Hormone
WHO - World Health Organization
DM - Diabetes Mellitus
IGT - Impaired Glucose Tolerance
IFG - Impaired Fasting Glucose
DFO - Deferoxamine
DFP - Deferiprone
DFX - Deferasirox
GH - Growth Hormone
IGF-1 - Insulin-like Growth Factor 1
HPT - Hypothalamic-Pituitary-Thyroid
HPG - Hypothalamic-Pituitary-Gonadal
MRI - Magnetic Resonance Imaging
TDT - Transfusion Dependent Thalassemia
NTDT - Non-Transfusion Dependent Thalassemia
RDA - Recommended Dietary Allowance
PTH - Parathyroid Hormone
ICET - International Network on Endocrine Complications in Thalassemia

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ABSTRACT

Background: Thalassemia major is one of the most common hereditary hemoglobinopathies worldwide, characterized by ineffective erythropoiesis and chronic hemolytic anemia. Regular blood transfusions, though life-saving, result in progressive iron overload affecting various organs including the endocrine glands. Despite advances in iron chelation therapy, endocrinopathies remain a significant cause of morbidity in thalassemia major patients.

Objective: To study the endocrine manifestations in children and adolescents with thalassemia major and to identify associated risk factors.

Methods: This study included 51 children and adolescents with thalassemia major attending the thalassemia clinic. Detailed history, anthropometric assessment, clinical examination, and laboratory investigations including complete blood count, serum ferritin, glucose parameters (FBS, PPBS, RBS, HbA1c), thyroid function tests (T3, T4, TSH), serum calcium, and gonadotropin levels (LH, FSH) were performed.

Results: The study population comprised 58.8% males and 41.2% females, with 62.7% aged 5-10 years. 74.5% had initiated transfusions before one year of age, and 88.2% received monthly transfusions. Growth retardation was evident with 23.5% having weight and 29.4% having height below the 3rd centile. Endocrine abnormalities included diabetes (25.5%), pre-diabetes (33.3%), hypothyroidism (9.8%), hypogonadotropic hypogonadism (25% with low LH and 12.5% with low FSH), and hypocalcemia (21.6%). Serum ferritin was elevated (>1500 ng/mL) in 90.2% of patients. Significant associations were observed between HbA1c levels and chelation therapy ($p<0.001$), hypogonadism with chelation therapy ($p=0.005$).

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Conclusion: Endocrine complications are common in pediatric thalassemia major patients, with glucose metabolism abnormalities being the most prevalent. Age, transfusion burden, and chelation therapy significantly influence the risk of endocrinopathies. Regular monitoring of endocrine function and appropriate intervention are essential for improving quality of life and reducing morbidity in these patients.

Keywords: Thalassemia major, Endocrine manifestations, Iron overload, Diabetes mellitus, Thyroid dysfunction, Hypogonadism, Children, Adolescents, Chelation therapy

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INTRODUCTION

Thalassemia major represents one of the most prevalent monogenic disorders globally, characterized by defective haemoglobin synthesis leading to severe anaemia that necessitates regular blood transfusions for survival.¹ While these life-sustaining transfusions have dramatically improved life expectancy, they have inadvertently given rise to various complications, particularly those affecting the endocrine system. Iron overload, resulting from both repeated transfusions and increased gastrointestinal iron absorption, emerges as the primary culprit behind these endocrine complications.²

The impact of iron overload on endocrine glands presents a significant challenge in the management of thalassemia major, especially during the crucial periods of childhood and adolescence. Despite modern chelation therapy, endocrinopathies continue to be a major source of morbidity in these patients. The spectrum of endocrine complications is broad, encompassing growth retardation, delayed or absent pubertal development, hypothyroidism, hypoparathyroidism, diabetes mellitus, and adrenal insufficiency.³ These manifestations not only affect the physical development of young patients but also have profound implications for their psychological well-being and quality of life.

Growth disorders are particularly concerning, affecting approximately 30-50% of children with thalassemia major. The pathogenesis is multifactorial, involving chronic anaemia, iron overload in the growth hormone-insulin-like growth factor axis, and other endocrine complications.⁴ Pubertal disorders, another significant concern, affect up to 70% of patients, with hypogonadotropic hypogonadism being the most common

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endocrine complication. This high prevalence underscores the vulnerability of the hypothalamic-pituitary-gonadal axis to iron toxicity.⁵

The development of diabetes mellitus in thalassemia patients represents a unique pathophysiological process, distinct from both type 1 and type 2 diabetes. Iron deposition in pancreatic β -cells, combined with insulin resistance, creates a complex metabolic scenario that requires careful monitoring and management.⁶ Studies have shown that approximately 6-14% of children and adolescents with thalassemia major develop diabetes, with the risk increasing with age and transfusion burden.⁷

Thyroid dysfunction, manifesting as either subclinical or overt hypothyroidism, affects about 8-28% of patients, while hypoparathyroidism occurs in 1-22% of cases.⁸ These variations in prevalence across different studies highlight the need for systematic evaluation and regular monitoring of endocrine function in this vulnerable population. The timing and progression of these complications can vary significantly among patients, influenced by factors such as age at diagnosis, transfusion regimen, chelation therapy compliance, and genetic predisposition.

Moreover, the interrelationship between different endocrine complications creates a complex clinical picture that requires comprehensive evaluation and management. For instance, growth failure may be exacerbated by hypothyroidism or growth hormone deficiency, while delayed puberty can further impact final adult height.⁹ This intricate web of endocrine manifestations necessitates a holistic approach to patient care, with regular screening and early intervention being crucial elements in preventing or minimizing complications.

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Recent advances in chelation therapy, including the introduction of new oral chelators and combination therapy approaches, have shown promise in preventing and managing endocrine complications. However, the optimal timing of intervention and the most effective strategies for preventing endocrine dysfunction remain subjects of ongoing research. Additionally, the impact of newer chelation regimens on endocrine outcomes in children and adolescents requires further investigation.¹⁰

Understanding the pattern, progression, and risk factors associated with endocrine complications in thalassemia major is crucial for developing effective screening protocols and preventive strategies. This is particularly important in the paediatric and adolescent population, where early intervention can significantly impact long-term outcomes. Regular monitoring of endocrine function, coupled with appropriate interventions, can help minimize the impact of these complications on growth, development, and quality of life.

This prospective cohort study aims to comprehensively evaluate the spectrum of endocrine manifestations in children and adolescents with thalassemia major, focusing on their prevalence, progression, and associated risk factors. By understanding these patterns, we hope to contribute to the development of more effective monitoring and management strategies for this vulnerable patient population.

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AIM & OBJECTIVE

1. To study the prevalence of endocrine manifestations in patients with thalassemia major and to refer them for required endocrine treatment.

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REVIEW OF LITERATURE

A Historical Perspective of Thalassemia

The illness originally known as "Cooley's anaemia" was named for Dr. Thomas Benton Cooley, an American paediatrician who discovered identical symptoms in children of Italian and Greek ancestry while studying childhood anaemia in 1925. Beta thalassaemia major is the current name for this type of thalassaemia.

Since the condition was found to be more common in those whose ancestral homes surrounding the Mediterranean Sea, the term "thalassaemia," which is derived from the Greek word "thalassa," which means "of the sea," was chosen as the umbrella term..¹¹

1938-Thalassemia is recognized as a genetic disease.

1948-Thalassemia is determined to be caused by an abnormal hemoglobin.

1964-The thalassemia mutation is found to protect against malaria.

1975-Treatment with regular blood transfusions begins to improve patient survival.

1977- Prenatal diagnosis for thalassemia becomes available.

1977: Richard Propper finds that desferoxamine can be used to eradicate the iron toxicity brought on by repeated blood transfusions.

1982: Azacytidine has been shown to raise foetal haemoglobin in patients with thalassaemia. Thalassaemia is originally cured by bone marrow transplantation.

1998: It has been demonstrated that oral chelators, like deferiprone, are therapeutically useful in treating iron toxicity.

2001: Iron poisoning in the heart is detected via specialised radiological imaging. The

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hormone hepcidin, which regulates intestinal absorption of iron, is initially identified.

2003 saw the release of Deferasirox, a novel iron chelator.

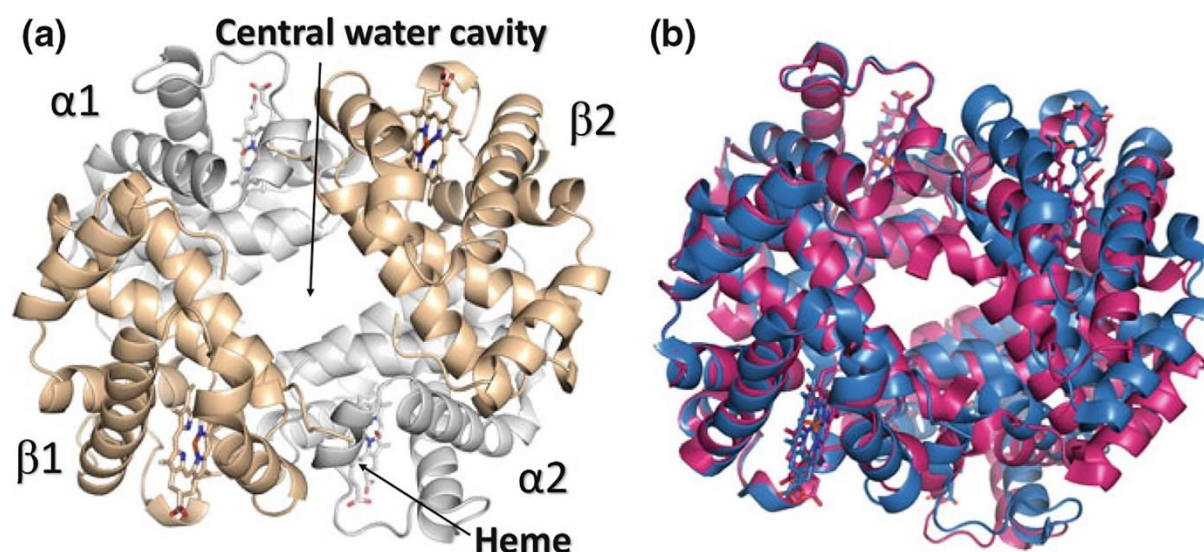
2007: A patient with beta thalassaemia, a more severe type of the condition, receives gene therapy for the first time.¹²

Normal Structure of Adult Haemoglobin

Each of the four subunits that make up haemoglobin has one heme group and one polypeptide chain.¹³ The prosthetic heme group iron protoporphyrin IX, which is linked to a polypeptide chain consisting of 141 (alpha) and 146 (beta) amino acid residues, is present in all haemoglobins.¹³ The N of a histidine is connected to the heme's ferrous ion. A phenylalanine in its polypeptide chain wedges the porphyrin ring into its pocket. Alpha and beta chains are the two types of polypeptide chains that make up adult haemoglobin; they differ in amino acid sequence but are comparable in length. All human haemoglobins, both embryonic and adult, have the identical alpha chain. The beta chain of normal adult haemoglobin ($\alpha_2\beta_2$), the gamma chain of foetal haemoglobin ($\alpha_2\beta_2$), and the delta chain of HbA₂ are examples of non-alpha chains. Two types of gamma chains are produced in certain variations due to the duplication of the gamma genes.¹³

Figure 1: The structure of haemoglobin crystals. The two α and β chains in the overall quaternary structure of Hb are tan and grey, respectively. b On top of the structure of deoxygenated (T state) Hb (blue) is the structure of oxygenated (R state) Hb (magenta).¹³

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Foetal Haemoglobin

The predominant kind of haemoglobin found in the foetus during pregnancy is called foetal haemoglobin (HbF). From 10 to 12 weeks of pregnancy to the first six months of postnatal life, erythroid precursor cells produce HbF. Haemoglobin A (HbA), the predominant form of adult haemoglobin, has two alpha and two beta subunits, whereas HbF has two alpha and two gamma subunits. The beta chain locus on chromosome 11 contains the genes that produce gamma chain proteins. The neutral, nonpolar amino acids alanine and glycine, which are found at position 136 of the gamma subunit, distinguish it from its adult counterpart. This variation causes the protein to undergo structural alterations, which results in a number of physiological variations in oxygen delivery that are crucial for foetal circulation.¹⁴⁻¹⁶

Thalassemias

Haemoglobin molecular abnormalities are among the most prevalent and clinically significant genetic illnesses.¹⁷ They can be divided into two main categories: thalassaemias, which are caused by mutations that affect the quantity of protein generated, and hemoglobinopathies, which are caused by structural changes to the haemoglobin molecule that produce a different protein.

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Definition

Reduced or absent synthesis of one of the two polypeptide chains (α or β) that make up the normal adult human haemoglobin molecule (haemoglobin A, α_2/β_2) is a characteristic of the recessively autosomal inherited conditions known as thalassaemias, which leads to anaemia and decreased haemoglobin in red blood cells.¹⁸

Burden of Disease

It is unknown how many patients are impacted. In many nations, children pass away from the more severe transfusion-dependent disorders before they are ever diagnosed, and very few countries keep a patient register. An estimated 60,000 births per year are anticipated worldwide.¹⁷ From the Mediterranean basin and Sub-Saharan Africa via the Middle East and the Far East, which includes South China and the Pacific Islands, the thalassaemia genes are distributed. These genes are uncommon in indigenous communities in northern regions, but population shifts brought on by political unrest and economic factors are also influencing the epidemiology.^{19, 20}

An estimated 80 million people worldwide are carriers of β -thalassemia, and 300–400 thousand children are born each year with inherited significant haemoglobin disorders.^{21, 22} Three clinical states of thalassaemia with increasing disease severity have been recognised. These include thalassaemia major, thalassaemia intermedia, and the β -thalassemia carrier condition.

Heterozygosity for β -thalassemia causes the development of the β -thalassemia carrier state, which has distinct haematological features and no clinical symptoms.²³ The South Asian countries of Bangladesh, India, and Pakistan are thought to account for a significant portion of β -thalassemia carrier instances among these global populations.²⁴ According to the majority of establishmentarians, at least 5.2% of the world's population, or more than 300–360 million

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people, have haemoglobin that is structurally abnormal.^{25, 26} Approximately 80–90 million people worldwide are β -thalassemia carriers, making up 1.5% of the global population.

Furthermore, an estimated 68,000 babies with β -thalassemia, both minor and significant, are born each year, according to reports.²⁷ The number of people who are carriers of thalassaemia varies by nation. About 60% of people in Bangladesh, 6.8%–12.8% of people in Malaysia, and almost 40% of people in Thailand are affected.²⁹ According to several studies, 90% of children with thalassaemia major are born in low- or middle-income countries (LMICs), with about 23,000 of them having the condition.³⁰

Aetiology

Since thalassaemia is autosomal recessive, the condition cannot be passed down to the following generation unless both parents have it or are carriers. Alpha or beta chains are either absent or produced insufficiently as a result of mutations or deletions in the Hb genes. More than 200 mutations have been found to be the cause of thalassaemias.³¹

Types

Alpha-globin gene deletion causes alpha thalassaemia, which is characterised by decreased or nonexistent alpha-globin chain production. There are four alleles of the alpha globin gene, and the number of allele deletions determines how severe the condition is. The most severe type, known as four allele deletion, results in the formation of tetramers from excess gamma chains that were present during the foetal stage and the absence of alpha globins. It causes hydrops fetalis and is incompatible with life. The mildest type, one allele loss, is largely clinically quiet.

Point mutations in the beta-globin gene cause beta thalassaemia. Based on the beta-gene mutation's zygosity, it is separated into three groups.³¹ Beta-thalassemia minor, which is caused

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by a heterozygous mutation (beta-plus thalassaemia), is characterised by underproduction of beta chains.³¹ It is typically asymptomatic and mild³¹. A homozygous mutation of the beta-globin gene causes beta thalassaemia major, which is characterised by the complete lack of beta chains. Clinical symptoms include hepatosplenomegaly, growth retardation, jaundice, endocrine disorders, and severe anaemia that necessitates lifelong blood transfusions.³¹ Beta-thalassemia intermedia is a disease that falls between these two kinds and has mild to moderate clinical symptoms.

- One gene mutation: little symptoms. Thalassaemia minor is the name of the condition.
- There will be moderate to severe signs and symptoms due to two mutant genes. This disorder is known as Cooley anaemia or thalassaemia major. Usually healthy at birth, babies with two mutant beta haemoglobin genes begin to show symptoms six months later when adult haemoglobin replaces the foetal haemoglobin (Hb-gamma).

Beta-thalassemia is caused by an excess of unpaired alpha-globin chains that collect and produce precipitates that harm red cell membranes and cause intravascular haemolysis. This early erythroid precursor cell loss causes inefficient erythropoiesis, which in turn causes haematopoiesis to expand extramedullarily.

Alpha thalassaemia coinheritance: Because of a less severe alpha-beta chain imbalance, beta-thalassemia patients who have this condition have a milder clinical history.

Sickle cell trait coexistence: Sickle cell disease symptoms arise when beta-thalassemia, a serious hemoglobinopathy, coexists with sickle cell trait. The predominant Hb in the co-existence state is HbS, which makes up about 60% of Hb depending on the disease type (beta-zero or beta-plus0), in contrast to sickle cell trait, where the major Hb is HbA.

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Another prevalent Hb variation in Southeast Asian populations is haemoglobin (HbE). Given that HbE is frequently detected in thalassaemia patients in this region, it is associated with a beta-thalassemia phenotype.

Transfusion-requiring and non-transfusion-requiring thalassaemias are two new terms that are being used increasingly frequently in clinical settings. All of the fundamental classifications fit into these two categories based on whether or not frequent blood transfusions are required..³²⁻³⁴

BETA THALASSEMIA

Pathophysiology

The effects of excess, unpaired α -globin are seen in erythropoiesis in people with β -thalassemia.³⁵⁻³⁷ In fact, rather than haemoglobin underproduction, the primary determinant of illness severity is the degree of imbalance in the α -globin against $\beta + \gamma$ -globin biosynthesis ratio.^{35,36,38} The severe phenotype of individuals with β^0 -thalassemia mutations is caused by a substantial chain biosynthetic imbalance.³⁶

Before being released to interact with β -globin to create the haemoglobin tetramer, α -globin first forms a protein complex with its molecular chaperone, α -hemoglobin stabilising protein (AHSP), after synthesis.^{39,40} AHSP promotes α -globin folding and inhibits the development of misfolded aggregates. Human microcytosis and anaemia are linked to α -globin mutations that affect interaction with AHSP.⁴¹ In a mouse model of β -thalassemia, it has also been demonstrated that loss of AHSP affects erythropoiesis.⁴² The phenotype of β -thalassemia may be influenced by AHSP levels, according to evidence.⁴³

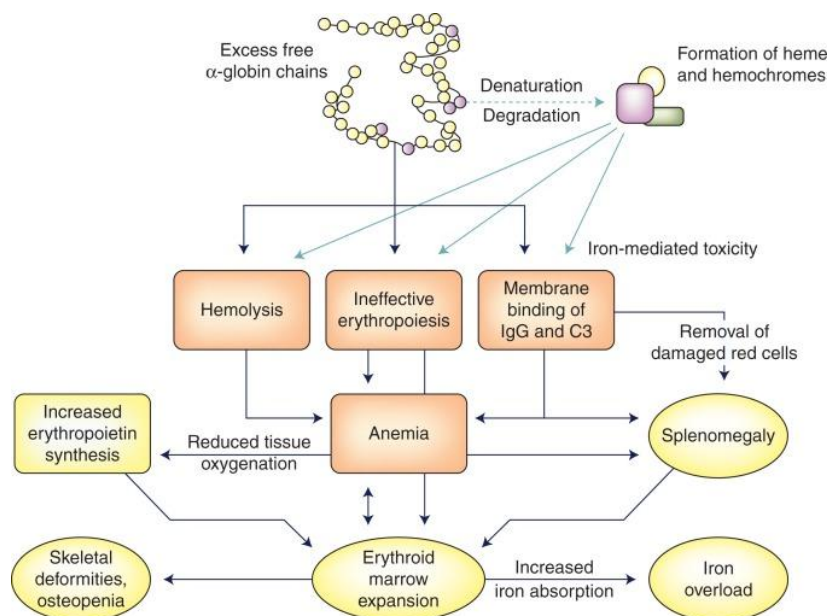
“When AHSP's capability is surpassed, α -globin aggregates into molecular aggregates that precipitate and produce inclusions that harm intracellular organelle membranes and cell

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membranes. Additionally, reactive oxygen species are produced by aggregating α -chains, further harming the lipid and protein components of cell membranes. In addition to heme and iron, hemichromes—one of the most hazardous byproducts of unpaired α -chains—bind to the membrane and encourage the clustering of band 3, one of its main components.⁴⁴ Early in erythropoiesis, α -chain inclusions are formed, peaking in polychromatophilic erythroblasts and causing cellular death.⁴⁵ Therefore, anaemia in severe β -thalassemias is a result of both reduced red cell survival due to α -globin inclusions and inefficient erythropoiesis.^{35,36} The pathogenesis of Huntington's disease and Parkinson's disease, which are brought on by buildups of unstable, aggregation-prone proteins, has been compared to that of β -thalassemia.⁴⁶ Nearly every cell has the ability to detoxify and eliminate harmful proteins through a variety of biochemical processes known as protein quality control (PQC). Although it is believed that the ubiquitin–proteasome system (UPS) and the lysosome-autophagy pathways involved in PQC contribute to the breakdown of α -globin, the erythroid cells of people with severe types of β -thalassemia surpass the capabilities of these processes.”

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Figure 2: Pathophysiology of β Thalassemia



Genetic modifiers

At the molecular level, the thalassaemias are diverse; over 200 mutations that cause the disease have been found.^{37, 44, 47} Promoter mutations are commonly found in alleles with mild phenotype, although splicing and frameshift mutations have also been found in people with moderate phenotype who are homozygous for β -thalassemia. Another method that lessens the phenotype of homozygous β -thalassemia is the inheritance of an α -thalassemia gene.⁴⁸ In those with β -thalassemia, foetal haemoglobin is a significantly more prevalent and significant modulator of disease severity. Only a small percentage of erythroid cells in healthy people synthesise HbF. HbF makes up only 5–8% of red blood cells, or F cells, which account for 5%–20% of the cells' total haemoglobin.⁵⁰ “Even low levels of γ -globin in F cells can reduce the relative excess of α -globin in the context of a severe β -globin synthesis deficiency. This gives cells that produce HbF a strong selective survival advantage in the context of the ineffective

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erythropoiesis that characterises the most severe forms of β -thalassemia.” It is believed that a considerable proportion of patients who are homozygous for β -thalassemia have elevated levels of foetal haemoglobin percentage, which can be explained by this selective survival.⁵¹ Increased γ -chain synthesis from the same chromosome is linked to certain mutations in the β -globin promoter.³⁷ Normal people and perhaps those with β -thalassemia have different numbers of F-cells, which are controlled by genetics.⁵² A milder clinical phenotype is presumably linked to F-cell counts that fall within the greater range of normal. Coinheritance of an HPFH gene has been linked to increased mean corpuscular haemoglobin, mean corpuscular volume, and HbA2 levels, according to a large pedigree analysis.⁵³ HbF levels and the frequencies of morbidities that indicate the severity of the disease are inversely correlated, according to a recent study conducted in untransfused patients with thalassaemia intermedia.⁵⁴ Hydroxyurea has been shown to lower the need for transfusions in a small percentage of patients receiving regular transfusions and to raise HbF in certain untransfused patients with severe β -thalassemia.⁵⁵ Some haplotypes of thalassemic individuals may be more likely to have a favourable response to hydroxyurea.⁵⁶

“Genome-wide association studies (GWAS) have shown other loci that can significantly contribute to the variation in HbF levels, in addition to SNPs within the β -globin locus.”⁵² It has been demonstrated that an SNP in the BCL11A gene influences the degree of HbF expression. Functional investigations have demonstrated that BCL11A plays a crucial role in the silencing process that inhibits the γ -globin genes, as Sankaran and Orkin⁶¹ describe.⁶² HbF synthesis is significantly increased in cultured thalassemic erythroid cells when BCL11A levels are suppressed.⁶³ There is experimental evidence that Bcl11a suppression can repair sickle cell disease in a mouse model.⁶⁴ The key area that distinguishes HPFH from deletions in $\delta\beta$ -

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thalassemia is one of the places in the region between the $A\gamma$ - and δ -globin genes where BCL11A interacts.⁵⁸ MYB is another locus that has been linked to regulating HbF levels. 52 Variations in the degree of MYB expression are linked to an SNP in what is believed to be a regulatory region close to the gene. HbF levels are higher in those with lower MYB levels than in those with higher MYB levels. In a another study, elevated HbF levels were linked to a 3-bp deletion in an intragenic region close to the MYB gene with enhancer-like activity. It has been demonstrated that in people homozygous for Sardinian β^0 -thalassemia, variations in both the BCL11A and MYB loci alter the severity of the condition. HbF level regulation has been linked to additional transcription factors, such as KLF1.⁶³ KLF1 may use a dual mechanism that acts on the BCL11A and β -globin promoters to mediate its effects on HbF.

Due to persistent haemolysis and inefficient erythropoiesis, people with thalassaemia suffer hyperbilirubinemia. Blood transfusions and enhanced iron absorption are the two main causes of iron loading. Osteoporosis is widespread and may be caused by marrow cavity growth, hypogonadism, and other endocrine disorders. The severe variants of β -thalassemia are also characterised by increased vulnerability to infection. It has been reported that genetic variations in a number of genes linked to these clinical characteristics function as tertiary modifiers of the thalassaemia phenotype.⁵⁷

Iron overload

“Increased tissue deposition of iron is seen in patients with the most severe forms of β -thalassemia, including intermedia and major.” Iron deposition occurs in the reticuloendothelial system when transfusion-dependent β -thalassemia patients experience senescence of transfused red blood cells. Dedeposited iron also develops in the hepatic parenchyma, different endocrine tissues, and, at a slower rate, the heart as iron overload worsens.

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Controlling absorption is how normal persons maintain iron homeostasis.⁶⁵ The body loses only around 1 mg every day, mostly as a result of the epithelial cells of the skin, colon, urinary system, and other mucosal organs shedding.⁶⁵ “After red cell senescence, receiving a unit of packed red blood cells usually results in the deposition of 200 mg of iron in the tissues.” This is because each millilitre of transfused blood contains around 1 mg of iron.⁶⁵ People with thalassaemia who get blood transfusions invariably suffer from severe iron overload because they lack excretory mechanisms.⁶⁵

Increased tissue iron in people with thalassaemia intermedia mostly results from increased iron absorption, though it can also happen as a result of sporadic transfusions.⁶⁶ “The release of erythroid components during cellular apoptosis linked to inefficient erythropoiesis, which prevents the liver from producing hepcidin, is likely the cause of this paradoxical increase in iron absorption despite systemic iron overload.”⁶⁷ The 25-amino-acid peptide hormone hepcidin inhibits the release of stored iron from hepatocytes, the release of iron from macrophages, and the absorption of iron from food, hence adversely regulating the flow of iron into the plasma.⁶⁷ The iron exporter ferroportin is a multipass transmembrane protein that allows ferric iron to leave cells. All known iron-exporting cells, including hepatocytes, splenic and hepatic macrophages, and duodenal enterocytes, are rich in ferroportin.⁶⁷ By binding ferroportin and causing both molecules to be endocytosed, followed by lysosomal breakdown, hepcidin prevents iron efflux.⁶⁸ Growth differentiation factor 15 (GDF15), a member of the transforming growth factor- β superfamily, is one of the factors secreted by apoptotic erythroblasts. Primary human hepatocytes' synthesis of hepcidin was decreased by serum from thalassaemia patients, and this suppression was not triggered by GDF15 deficiency. It has also been demonstrated that a second molecule, called twisted gastrulation (TWSGI), is extensively produced in erythroblasts and has

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the ability to suppress the expression of hepcidin in both human and animal erythroid cells.⁶⁹

The functions of TWSGI and GDF15 are still unclear. Iron release from macrophages and improved intestinal absorption are the ultimate outcomes of hepcidin expression inhibition. A recent review examined the regulation of hepcidin production in both normal and pathological conditions.⁷⁰ Longer half-lived synthetic mini-hepcidins have been suggested as possible treatment agents for people with severe β -thalassemia and have been demonstrated to decrease iron absorption in mice following oral administration.⁷¹

“Cell-released iron is attached to transferrin and carried to the bone marrow and other tissues, where the transferrin receptors absorb the iron.”⁷² Although up to 25 mg of transferrin-bound iron may circulate over the 24-hour cycle, less than 1% of the body's iron is detected in blood at any given moment.”⁷² People with β -thalassemia have increased erythropoiesis, which causes their plasma iron turnover to rise dramatically by 10–15 times over normal.⁷² Typically, the transferrin saturation is kept between around 10% and 50%. “Ferritin, a multicomponent protein shell that internalises iron and shields cellular components from possible oxidative damage, is the form of iron that is retained in tissue.” The cytosolic soluble iron pool and intracellular ferritin iron are in balance. When ferritin is broken down in lysosomes, an insoluble iron aggregation known as hemosiderin is created.⁷³ In those with severe β -thalassemia, ferritin and hemosiderin build up in their cells. While iron buildup in parenchymal tissues can impair vital cells in the liver, endocrine glands, and heart, it is rather innocuous in reticuloendothelial cells.⁷² “Transferrin saturation rises to 75% to 100% and non-transferrin-bound iron (NTBI) is detected in the blood as a result of iron overload in thalassaemia patients, which can be caused by blood transfusions, excessive absorption, or a combination of the two.”⁷⁴ Being highly diverse, NTBI can take many different forms, including complexing with proteins and citrate.⁷⁵ Methods for

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identifying labile plasma iron (LPI), a portion of the NTBI pool that interacts metabolically with membrane components and damages membranes by producing reactive oxygen species (ROS), have been developed.⁷⁶ Instead of using the transferrin receptor, NTBI reaches cells through a variety of cellular pathways in potentially harmful forms.⁷⁷ NTBI is cleared by the liver and heart 200 times faster than transferrin-bound iron. While iron-mobilizing agents may be required to chelate more iron, iron chelators can directly reach a portion of the NTBI. Patients with thalassaemia may see a decrease in NTBI when given chelators.⁷⁷ Compared to subcutaneous administration, intravenous administration reduces NTBI more effectively. “Although these studies support the use of continuous rather than intermittent chelation in high-risk individuals, the dynamics of NTBI decrease and reemergence are fairly complex.” Heart myocytes are a crucial target for iron-induced ROS, as will be covered in more depth below.⁷⁷ The oral chelators deferasirox and deferiprone efficiently accessed and decreased the intracellular labile iron compartments using an in vitro model of newborn rat cardiomyocytes, while desferrioxamine mostly eliminated the LPI in plasma to remove iron. According to these in vitro investigations, oral chelators may be effective in preventing and reversing the heart damage brought on by iron overload because of their quick access to intracellular labile iron compartments.⁷⁹

Forms of Beta Thalassemia⁸⁰

Heterozygous Beta Thalassemia

Microcytosis, hypochromia, and typically a rise in the proportion of HbA2 are the haematological characteristics of thalassaemia trait. 92%–95% HbA, >3.8% HbA2, and varying levels of HbF (0.5–4%) make up the haemoglobin composition.⁸⁰ Apart from microcytosis and hypochromia, red blood cells exhibit significant size and shape variation, with the mean corpuscular volume of β^0 -thalassemia trait red blood cells being lower than that of β^{+-}

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thalassemia trait red blood cells.⁸⁰ It has long been believed that the mild anaemia with microcytic, hypochromic red blood cells that characterises the thalassaemia trait has no clinical implications beyond its correlation with pregnancy-related anaemia.⁸⁰ However, despite having haemoglobin levels that fall within the normal range, people with thalassaemia trait may still have anaemia symptoms as headache, lethargy, weariness, dizziness, and exercise intolerance, according to a newly conducted controlled trial conducted in Sri Lanka.⁸⁰ The two groups that had either moderate anaemia or haemoglobin levels within the normal range did not differ in the frequency of these symptoms. Those with β -thalassemia phenotype also experienced a markedly higher frequency of infectious episodes. Men with thalassaemia trait experience myocardial infarction later in life, and they are less likely than women to have extensive coronary artery disease.⁸⁰

Homozygous Beta Thalassemia

Patients with homozygous β -thalassemia have a very diverse range of symptoms.⁸⁰ Many people get severe anaemia at a young age and are dependent on transfusions for the rest of their lives. These people have been diagnosed with thalassaemia major. Some people with homozygous β -thalassemia have varying degrees of anaemia and may occasionally need transfusions, while others have milder anaemia and never need one.⁸⁰ They are classified as having thalassaemia intermedia. People with thalassaemia intermedia can have anaemia that ranges from almost normal to severe enough to occasionally need blood transfusions. Osteoporosis and medullary enlargement with facial deformities are caused by erythroid hyperplasia, and they can be fairly severe.⁸⁰ The paraspinal and pulmonary masses of erythroid cells, as well as the liver and spleen, expand as a result of extramedullary haematopoiesis.⁸⁰ The major versus intermedia syndrome diagnostic criteria are not well defined and are mostly dependent on haemoglobin levels without

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transfusion. A cutoff of 7 g/dL is typically used to differentiate between the two types, but this criterion is complicated by the fact that individual patients may have varying degrees of anaemia, splenomegaly, and defective development at different times, and that the use of transfusion is partially determined by socioeconomic factors in addition to access to a sufficient blood supply. According to a comprehensive assessment of the subject, the diverse spectrum of β -globin locus mutations, several secondary and tertiary modifiers, and a variety of environmental factors all contribute to the amazing phenotypic diversity of β -thalassemias.⁸⁰

History and Physical Examination

Usually, beta-thalassemia minor is found by chance during a regular full blood count. Patients may exhibit moderate anaemia symptoms without any notable physical examination findings.

If the diagnosis has not been made prenatally, patients with beta-thalassemia major (TM) manifest between 6 and 24 months of age, at which point their haemoglobin production changes from foetal (HbF) to adult (HbA). The result is severe anaemia, which manifests as pallor, diarrhoea, irritability, feeding difficulties, failure to thrive, frequent fever episodes, and hepatosplenomegaly-induced belly enlargement. “Growth retardation, jaundice, brown skin pigmentation, poor musculature, genu valgum, hepatosplenomegaly, leg ulcers, development of masses from extramedullary haematopoietic sites, and skeletal deformities from bone marrow expansion are all consequences of untreated or inadequately treated infants, particularly in resource-poor areas.”⁸¹ Common skeletal abnormalities include long bone malformations, maxillary enlargement, and frontal bossing.⁸¹

Although beta-thalassemia intermedia can manifest in a variety of ways, it is by definition not severe enough to necessitate frequent transfusions. Children as early as two years

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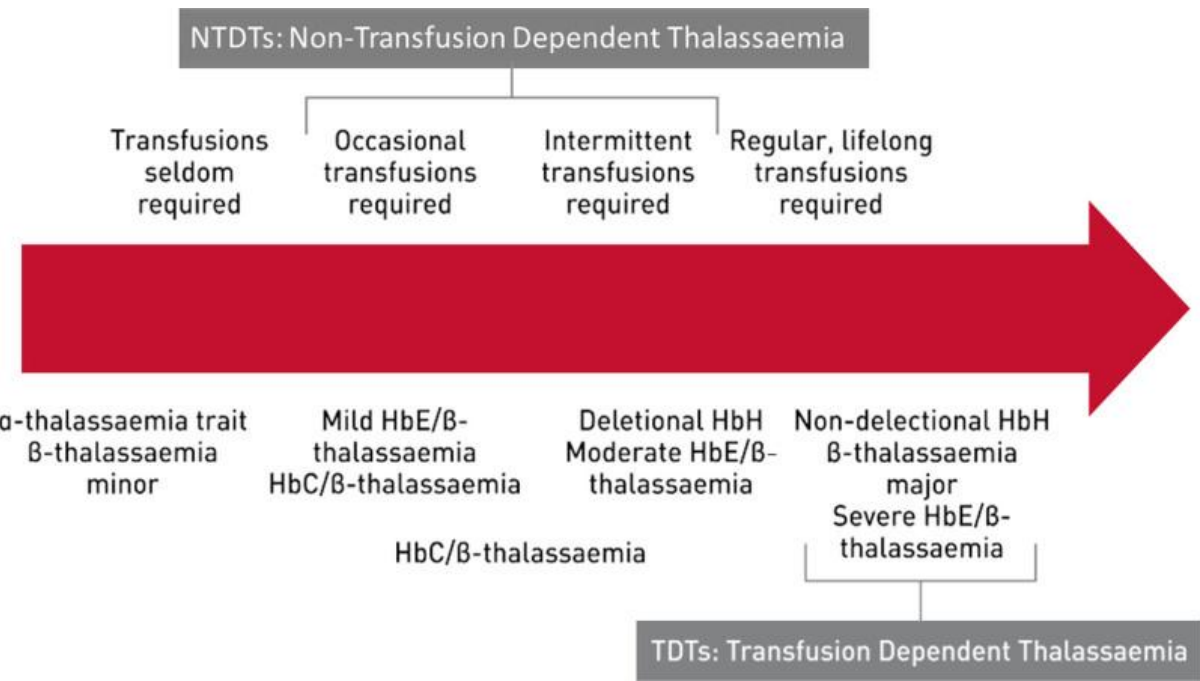
old may have growth and developmental delays due to intermedia. Adults with milder types of beta-thalassemia intermedia may initially exhibit pallor and tiredness.

Table 1: Thalassemia Groupings According to Clinical Severity.⁸³

α -Thalassemia hydrops fetalis	Leads to death in utero in most cases
Transfusion-dependent (β) thalassemia	Leads to death in early infancy unless treated
Non transfusion-dependent thalassemia	Occasional blood transfusions required (may become transfusion-dependent in later life)
Thalassemia minor	Mostly heterozygotes for thalassemia genes (carriers), but may include some homozygotes/compound heterozygotes for very mild β -thalassemia mutations and HbE

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Figure 3: Thalassemia Syndrome Phenotypic Classification by Clinical Severity and Transfusion Need⁸³



Manifestations of Iron Overload

The clinical profile of those with severe β -thalassemia is now dominated by the clinical signs of iron overload. The primary clinical issue that might cause premature mortality is heart malfunction. Significant issues also arise from endocrine imbalances, specifically hypogonadism, low growth hormone, hypothyroidism, and diabetes mellitus. Liver iron deposition can be significant, although unless iron overload is quite severe, functional impairments are often minor. Thankfully, iron overload issues can be avoided and even reversed with chelation therapy when used in conjunction with thorough combination therapy.⁸⁴

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“Noninvasive Measurement of Tissue Iron”

“Hepatic biopsies and liver iron content testing have long been the gold standard for assessing the degree of iron overload in people with severe β -thalassemia. Magnetic susceptibility imaging was the first noninvasive quantitative technique to establish a connection between magnetic susceptibility imaging and liver iron levels determined by biopsy.”⁸⁵ This methodology has not been widely applied since just a few universities possess the required tools. Only when liver iron concentration could be precisely measured by magnetic resonance imaging (MRI) using clinically available tools that could be standardised from institution to institution did noninvasive evaluation of liver iron replace hepatic biopsy as the gold standard.”⁸⁶

“MRI has also been used to assess cardiac iron. The degree of iron overload in the liver and, by extension, the iron content of the myocardium have been shown to be correlated with the $T2^*$ parameter and its reciprocal $1/R2^*$. A few autopsy investigations support a direct correlation between MRI measurements and chemically determined myocardial iron. MRI has also been used to evaluate iron buildup in the pituitary and pancreatic. The advent of these noninvasive techniques has facilitated the determination of the relative rate of iron mobilisation from various tissues during chelation therapy. Compared to the heart and endocrine tissues, which mobilise iron far more slowly, the liver does it more readily.”⁸⁷

Cardiac Manifestations

Patients with thalassaemia major can avoid the obvious effects of anaemia by receiving regular transfusions. Iron buildup, on the other hand, worsens in the late teens or early twenties due to iron deposition in the heart and toxic NTBI in the plasma. Congestive heart failure and/or atrial and ventricular arrhythmias are examples of cardiac abnormalities.⁸⁸ While some patients passed away from progressive congestive heart failure, sudden death frequently happened. By

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the middle of the 1920s, death was common.

Regular chelation with desferrioxamine changed this depressing clinical trajectory, especially when administered by continuous subcutaneous infusion for a considerable amount of each 24-hour period. It should come as no surprise that participants' adherence to the laborious subcutaneous delivery via a tiny infusion pump varied greatly, offering an unforeseen chance to contrast people who were well-chelated with those who were not.⁸⁹ One of the earliest clear indications that chelation therapy could alter the clinical picture with regard to the cardiac symptoms of iron overload was the marked decrease in cardiac mortality in well-chelated groups. The use of continuous chelation to prevent cardiac mortality has been well confirmed by subsequent big investigations.⁸⁷

Desferrioxamine continuous interfusion was the first treatment to improve existing heart disease. MRI T2* measurements demonstrated that iron was mobilised from the liver more easily than the heart. “According to a randomised trial, desferrioxamine and deferiprone administration together are more effective than desferrioxamine alone in reversing cardiac dysfunction, and there is evidence that the low-molecular-weight chelator deferiprone facilitates the mobilisation of iron from the myocardium.” It has also been demonstrated that deferasirox prevents and lessens myocardial iron overload.⁹⁰

The problem of pulmonary hypertension in patients with severe β -thalassemia is becoming more widely recognised. The two main risk factors that have been identified are advancing age and a history of splenectomy. Red cell membrane disease, oxidative stress, platelet activation, coagulation problems, and chronic haemolysis with thrombogenic vesicle release are some of the pathophysiological causes. While thalassaemia intermedia patients are more likely to have pulmonary hypertension, a recent cross-sectional study revealed that smoking, splenectomy, age,

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and hepatitis C infection are important univariate risk factors for pulmonary hypertension in both adults and children. When pulmonary hypertension is present, it can exacerbate heart failure brought on by left ventricular dysfunction and increase the severity of cardiovascular symptomatology.⁹¹

Endocrine Abnormalities

In β -thalassemics, iron excess usually manifests first as hypogonadism and growth retardation, partly due to growth hormone insufficiency. It was highly usual for unchelated patients to not develop secondary sex traits during adolescence. Even though hormone replacement is frequently necessary, regular chelation therapy has decreased the frequency of hypogonadism. 87 Women with severe β -thalassemia can become mothers with or without obstetrical intervention, while well-chelated young males with thalassaemia are fertile, though they may need hormonal treatment. Growth hormone insufficiency, hypothyroidism, hypoparathyroidism, and reduced glucose tolerance and diabetes are other endocrine problems.⁹²

Hepatic Manifestations

Patients with severe β -thalassemia are characterised by progressive iron deposition. The relationship between liver iron levels and histological and functional problems has been demonstrated by invasive liver biopsies and, more recently, non-invasive techniques. Iron accumulation up to 7 mg/g liver (dry weight) appears to be well tolerated; nevertheless, fibrosis in the periportal regions and eventually outright cirrhosis develop as the liver iron concentration rises due to frequent transfusions and insufficient or nonexistent chelation. Until iron excess is severe, liver functional problems are minimal. Prior to the discovery of efficient screening, hepatitis C infection was widespread and may have hastened the development of cirrhosis and raised the chance of developing hepatocellular cancer. Although the elevated risk of

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hepatocellular cancer due to hepatic iron excess is not entirely removed, chelation therapy minimises iron accumulation.⁹³

Other Complications

Patients with thalassaemia frequently develop osteoporosis, which is a result of marrow enlargement, endocrine deficits, iron toxicity, and possible chelator toxicity. Subclinical fractures, cortical thinning, and troublesome clinical fractures—the latter with little trauma—can all happen. Patients with thalassaemia have also been reported to have a hypercoagulable state due to endothelial cell activation, red cell membrane disruption, and platelet activation, which raises the risk of thromboembolism. persistent skin ulcers around the ankles as a result of persistent anaemia is another clinical symptom. Compared to patients with thalassaemia major who receive regular transfusions or patients with thalassaemia intermedia who are often transfused, untransfused individuals with thalassaemia intermedia are more likely to experience all of these problems. People with severe β -thalassemia frequently have nutritional deficits, which can lead to secondary issues like diabetes mellitus and osteoporosis. Although the exact role of osteoclast function inhibitors in thalassaemia is unknown, preliminary research indicates that they might be helpful.⁹⁴

Evaluation^{95, 96}

Beta-thalassemia major (TM) is the clinical diagnosis for children under two who have moderate jaundice, hepatosplenomegaly, and microcytic anaemia.

A complete blood count (CBC) showing haemoglobin levels below 7 g/dl, a mean corpuscular volume (MCV) between 50 and 70 fl, and a mean corpuscular haemoglobin (MCH) between 12 and 20 pg would all suggest microcytic hypochromic anaemia in a patient with beta-thalassemia major. MCV ranges from 50 to 80 fl, MCH ranges from 16 to 24 pg, and 95 Hb levels in beta-

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thalassemia intermedia vary from 7 to 10 g/dl. In beta-thalassemia minor, red cell counts are often higher, MCV and MCH are lower, and the red cell distribution width (RDW) is typically low. 96 The normal to slightly elevated RDW of thalassaemias helps differentiate them from other microcytic hypochromic anaemias, such as sideroblastic anaemia and iron deficiency anaemia, where the RDW is typically rather high. The peripheral blood smear will show microcytic hypochromic anaemia with target cells, teardrop cells, and often coarse basophilic stippling. In severe cases of beta-thalassemia, there is anisopoikilocytosis with abnormal red cell morphology and a high proportion of nucleated red blood cells. ^{95,96}

Peripheral smear and CBC results are non-specific. Haemoglobin electrophoresis or high-performance liquid chromatography (HPLC) must show aberrant percentages of HbA, HbA₂, and occasionally HbF in order to diagnose beta-thalassemia. Beta-thalassemia often manifests as a lower HbA percentage and a little elevated HbA₂; less than 10% have varying levels of HbF. Instead of beta-thalassemia, variable haemoglobin is suggested by a HbA₂ level exceeding 10%. The affected person's genetic composition determines how much HbA is reduced. Patients with homozygous beta (0) will not produce any HbA, while those with beta (+) alleles will have varying levels of HbA. The hallmark of beta-thalassemia minor is elevated HbA₂ (4–8%) and varying normal-to-low levels of HbF. Usually, beta-thalassemia major is characterised by normal to slightly raised HbA₂ and significantly elevated HbF (30–greater than 95%). There are no diagnostic laboratory results to distinguish between beta-thalassemia major and intermedia; this is a clinical differentiation.

A concurrent iron deficit that conceals an underlying beta-thalassemia minor is a frequent confounding factor in haemoglobin electrophoresis. The electrophoresis pattern that results seems typical. The main finding in beta-thalassemia minor is the HbA₂ %, which is normalised

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in iron deficiency anaemia. Hyperthyroidism, vitamin B12/folate insufficiency, and antiretroviral medication are additional causes of increased HbA2 besides thalassaemia. Other hemoglobinopathies that complicate a beta-thalassemia trait can also be clarified by haemoglobin electrophoresis and high-performance liquid chromatography.

Serum iron, ferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and % saturation of transferrin are also used in iron tests to rule out iron deficiency anaemia as the underlying cause.

Erythrocyte porphyrin levels can be assessed to distinguish an unclear diagnosis of beta-thalassemia minor from iron deficiency or lead poisoning. 96 Beta-thalassemia patients have normal porphyrin levels, but those with the latter diseases have elevated levels.

DNA analysis: These tests help confirm changes to the genes that make alpha and beta globin. DNA testing can be used to find carriers and help diagnose thalassaemia, albeit it is not a common procedure.

Because having relatives with thalassaemia mutations increases a person's likelihood of carrying the same mutant gene, family investigations may be necessary to ascertain carrier status and the types of mutations present in other family members.

In rare instances, amniotic fluid genetic testing may be useful when a foetus has a higher risk of thalassaemia. This is particularly important since it increases the likelihood that their child may inherit a combination of defective genes, which could result in a more severe form of thalassaemia, if both parents most likely have a mutation. Amniocentesis at 14–20 weeks gestation or chorionic villi sample at 8–10 weeks can be used for prenatal diagnosis in high-risk couples.

Figure 4: An overview of hemoglobinopathies and thalassaemia diagnostic techniques..⁹⁷

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		β-TM	β-TI	HbE / βThal	HbH
Hb levels		<5g/dL	~7 – 10 g/dL	Mild 9 – 12 g/dL Moderately/ Severe 6 – 7 g/dL Severe 4 – 5 g/dL	2.6 – 13.3 g/dL
BLOODSMEAR	Low Hb Production	Red cell hypochromia microcytosis, Target cells			
	Haemolysis	Irregularly crenated RBC, increased reticulocytes [5 – 10%]			
	Ineffective erythropoiesis	Nucleated RBC, Basophilic stripling			
	Special Features	+Numerous F-cells/ Acid elution	+F-cells/ Acid Elution	+DCIP staining [HbE] +F-cells/ Acid Elution	HbH inclusion bodies
Haemoglobin study		HbF up to 100% HbA2↑	HbF 10 – 50% [up to 100%] HbA2 > 4%	HbE [40 – 60%] HbF [60 – 40%] ±HbA [with β-thal] HbA2↑	Variable HbH [0.8 – 40%] HbA2↓ the presence of α-variants e.g. Hb CS, Hb PS etc.
DNA analysis		- Common known mutations of both β0 and β – thal mutations in population specific set can be done by PCR based methods. - For rare or unusual mutations, direct sequencing or array analysis is required - Other analysis for β-TI included α- and β- globin rearrangements, Xmn I polymorphism and other QTLs for γ-globin expression			
		Gap-PCR developed for 7 common α-thal deletions and RDB for non-deletional mutations. For unknown mutations, MLPA analysis and sequencing required			

ENDOCRINE ABNORMALITIES IN THALASSEMIA MAJOR⁹⁹

A common consequence of thalassaemia is endocrine problems. Issues like delayed sexual maturity and decreased fertility may continue even after proper chelation therapy is established early. Due to variations in the age at which chelation therapy is initially administered and the ongoing improvement in survival among patients who get effective chelation, it is challenging to estimate the prevalence of endocrine problems.

Growth

Thalassaemia major frequently results in growth retardation. Up until the age of nine or ten, when development velocity starts to reduce, growth patterns are largely normal. Chronic anaemia, transfusional iron overload, hypersplenism, and chelation toxicity may be major causes of stunted growth in thalassaemia patients. Hypothyroidism, hypogonadism, zinc deficiency, chronic liver disease, growth hormone insufficiency, undernutrition, and psychological stress are other contributing factors.

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Diagnosis and investigations

A thorough clinical evaluation is necessary for diagnosis in order to determine:

- Slow growth rates: growth velocity, as measured by growth velocity charts, is less than 1SD for both age and sex and is reported in cm/year.
- Short stature: according to national growth charts, height below the third centile for age and sex
- indications of further pituitary hormone deficits, such as gonadotrophins; and • additional potential reasons for growth retardation.

seeing a child with thalassaemia who exhibits stunted growth is typically comparable to seeing a child without the condition.

Evaluation of short stature/retarded growth

The first step in examining low stature or stunted growth is to measure standing and sitting height accurately and on a regular basis (every six months), as well as to assess bone age, pubertal staging, and metaphyses. The parents' height must be considered when interpreting absolute height.

Thyroid function tests (FT4, TSH), sex hormone levels, growth hormone (GH) release, zinc, calcium, alkaline phosphatase, urine analysis, and glucose tolerance research are other endocrine tests that might be useful. Insulin Growth Factor-I (IGF 1) and Insulin Growth Factor Binding Protein-3 (IGFBP-3) are two potentially helpful tests. The vast majority of thalassaemia patients have normal GH secretion. To rule out coeliac disease, however, a transglutaminase antibody test is also necessary.

Remember that one of the main causes of delayed growth is desferrioxamine toxicity (see Chapter on Iron load and Iron Chelation).

Treatment

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Traditional causes of poor growth in thalassaemia patients receiving irregular transfusions and those frequently using desferrioxamine include anaemia, folate insufficiency, and hypersplenism. Before beginning growth hormone treatment in peripubescent patients, hypogonadism should be thoroughly examined since it may lead to poor glucose tolerance and impaired insulin sensitivity. Patients with a confirmed zinc deficiency should get oral zinc sulphate supplements.

Delayed puberty and hypogonadism

Hypogonadism and delayed puberty are the most evident clinical effects of iron excess.

The total absence of pubertal development in females by the age of 13 and in boys by the age of 14 is known as delayed puberty. The absence of testicular enlargement (less than 4 ml) in boys and the absence of breast development in girls by the age of sixteen are considered indicators of hypogonadism.

In patients with thalassaemia who are moderately or severely iron overloaded, arrested puberty is a somewhat common consequence that is marked by a lack of pubertal progression for a year or longer. In these situations, the breast size is B3 and the testicular size stays between 6 and 8 ml. Annual growth velocity is either significantly decreased or nonexistent in these situations.

The majority of women with thalassaemia major experience primary amenorrhoea, and secondary amenorrhoea, especially in individuals with inadequate chelation, develops over time. In contrast to individuals with regular menstrual cycles, ovarian function is typically normal in these situations, but the gonadotrophin response to gonadotrophin-releasing hormone (Gn-RH) is low.

Investigations

Investigations for delayed puberty include routine biochemical analysis, bone age assessment via wrist and hand X-ray, thyroid function tests (TSH and FT4), and evaluation of hypothalamic-

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pituitary-gonadal function through Gn-RH stimulation testing for LH and FSH. Sex steroid levels (serum testosterone, 17- β , Estradiol) are measured alongside pelvic ultrasound to assess ovarian and uterine development. Transglutaminase antibodies are screened, while Growth Hormone stimulation testing and measurement of IGF-I, IGFBP-3, and plasma zinc levels may be performed in selected cases to thoroughly evaluate potential causes of pubertal delay.

Treatment

Age, the degree of iron overload, hypothalamo-pituitary-gonadal axis damage, chronic liver disease, and the existence of psychological issues brought on by hypogonadism all influence how hypogonadotrophic hypogonadism and delayed or stopped puberty are treated. Endocrinologists and other medical professionals must work together.

Girls may start treatment with oral ethinyl oestradiol (2.5–5 μ g daily) for six months, after which their hormones will be reassessed. Oral oestrogen is reintroduced for a further 12 months at progressively higher dosages (ethinyl oestradiol from 5 to 10 μ g daily) if spontaneous puberty does not occur within 6 months of the conclusion of treatment. The recommended course of treatment is low oestrogen-progesterone hormone replacement if breakthrough uterine haemorrhage does not occur.

Males with delayed puberty are treated with low doses of intramuscular depot-testosterone esters (25 mg) once a month for six months, after which their hormone levels are reassessed. A monthly dosage of 50 mg can be administered to patients with hypogonadotrophic hypogonadism until their growth rates start to decline. The intramuscular administration of 75–100 mg of depot-testosterone esters every 10 days is the fully virilising dose. Topical testosterone gel can produce the same results.

Testosterone esters or topical testosterone gel are used to treat pubertal arrest, same as they are

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for hypogonadotropic hypogonadism and delayed puberty.

Given the intricacy of the problems involved and the numerous complications that can arise, it is crucial that pubertal diseases be addressed patient-by-patient.

Hypothyroidism

This typically manifests in the second decade of life and can happen to people who are significantly anaemic and/or iron excess. In individuals receiving the best care, the problem is rare.

Signs and symptoms

There are no symptoms of preclinical hypothyroidism. Growth retardation, diminished activity, elevated weight, constipation, poor academic performance, heart failure, and pericardial effusion are some of the symptoms that can occur in mild and overt hypothyroidism. In women, the prevalence of hypothyroidism is somewhat higher. Thyroid ultrasonography typically displays an irregular echo pattern with thickening of the thyroid capsule, the thyroid gland is not palpable, and thyroid antibodies are negative.

It is advised that thyroid function be examined annually starting at age 12. Assessing bone age may be useful when assessing hypothyroidism. Primary thyroid dysfunction affects most people. Seldom does iron-mediated pituitary gland injury result in secondary hypothyroidism.

Treatment

With diligent chelation and good compliance, abnormal thyroid function may be reversed early on. The severity of organ failure determines the course of treatment. Intense iron chelation therapy and routine medical monitoring are necessary for subclinical hypothyroidism.

L-thyroxine is administered to patients with mild or obvious hypothyroidism.

Impaired carbohydrate metabolism

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The loss of β -cells due to iron overload, chronic liver disease, viral infection, and/or hereditary factors may result in impaired glucose tolerance and diabetes mellitus.

With a slower evolution of abnormalities in insulin secretion and glucose metabolism, as well as a similar age of commencement (it may begin early in the second decade of life), the pathophysiology is similar to type-2 diabetes.

Glycaemia can be categorised as normal, borderline, or diabetes.

- Diabetic type: plasma glucose 2 hours after a 75 g glucose load (2hPG) is ≥ 11.1 mmol/l (200 mg/dl) or fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl). Diabetic type is also indicated by a casual Plasma Glucose (PG) of ≥ 11.1 mmol/l (200 mg/dl). A person is diagnosed with diabetes if they continue to exhibit "diabetic type."
- FPG < 6.1 mmol/l (110 mg/dl) and 2hPG < 7.8 mmol/l (140 mg/dl) are considered normal.
- Borderline type: based on cut-off values for venous PG measures, this group comprises people who are neither diabetes nor normal types.

Ketoacidosis rarely complicates diabetes in thalassaemia.

Investigations

Every year since puberty, the Oral Glucose Tolerance Test (OGTT) should be conducted. The dosage for OGTT in children is 1.75 g/kg, up to a maximum of 75 g.

Treatment

A strict diabetic diet, weight loss when appropriate, and possibly intensive iron chelation therapy can improve impaired glucose tolerance. In patients with symptoms, insulin treatment is typically necessary but metabolic control may be challenging to achieve. When diet alone is insufficient to manage hyperinsulinism, acarbose may be a helpful first-line therapy for glycaemic control.

- It is still unclear how oral hypoglycemic medications function.

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Monitoring diabetes and its complications

Diabetic monitoring includes daily or alternate-day blood glucose measurements and ketone checks when blood sugar exceeds 250 mg/dl. Fructosamine estimation provides more valuable information than glycosylated hemoglobin levels, while urinary glucose monitoring is complicated by increased renal glucose threshold. Regular assessment includes renal function through serum creatinine testing, lipid profile evaluation (cholesterol: HDL, LDL, and triglycerides), urinary protein measurements, and screening for retinopathy to effectively track disease progression and prevent complications.

Hypoparathyroidism

One known late consequence of iron excess and/or anaemia is hypocalcaemia, which is caused by hypoparathyroidism and often manifests after the age of 16. Most patients exhibit paraesthesia along with a minor degree of the illness. Seizures, heart failure, or tetany may be seen in more severe cases.

Serum calcium, serum phosphate, and phosphate balance should all be examined starting at age 16. Parathyroid hormone should also be assessed in cases when serum calcium levels are low and phosphate levels are high. When 1,25 dihydroxycholecalciferol (vitamin D) values are low, parathormone levels might be either normal or low.

Bone radiography reveals deformities and osteoporosis.

Treatment

- Vitamin D or one of its equivalents administered orally. High dosages of vitamin D are necessary for certain people in order to return their serum calcium levels to normal. Given that hypercalcemia is a frequent side effect of this medication, this needs to be well watched.
- To return plasma calcium and phosphate levels to normal, 0.25–1.0 µg of calcitriol taken twice

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a day is typically adequate. At the beginning of treatment, weekly blood tests are necessary, followed by daily urine calcium and phosphate assays and quarterly plasma tests.

- A phosphate binder (other than aluminium) can be taken into consideration for patients whose serum phosphate levels are consistently elevated.
- Intravenous calcium treatment, followed by dietary vitamin D, is necessary for tetany and heart failure brought on by severe hypocalcaemia.

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Table 2: Pubertal assessment according to Tanner

Penile development	Breast development	Growth of pubic hair
P1: Prepubertal	B1: Prepubertal	PH1: Prepubertal
P2: Early puberty (enlargement of scrotum and testes, 4–5 ml, little or no enlargement of penis)	B2: Early puberty (breast bud stage)	PH2: Early puberty (sparse growth)
P3: Mid-puberty (enlargement of penis and further growth of testes, 8–12 ml, and scrotum)	B3: Mid-puberty (breast and areolar enlargement)	PH3: Mid-puberty (hair extends over the pubic junction)
P4: Advanced puberty (enlargement of penis in length and breadth. Increased pigmentation of scrotal skin and enlargement of testicles, 15–25 ml)	B4: Advanced puberty (areola and nipple project separately from the contour of the breast)	PH4: Advanced puberty (hair corresponds to adult growth but less extensive)
P5: Adult	B5: Adult (Fully developed breast, the areola no longer projects separately from the breast contour)	PH5: Adult

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Table 3: Hypothyroidism and its treatment

Hypothyroidism	Serum FT4	Serum TSH	TSH Response to TRH	Treatment
Subclinical	Normal	Marginally increased (TSH: 4.5–8mIU/l)	Increased	Observation
Mild	Marginally low	Elevated	Exaggerated	L-thyroxin
Overt	Low	Elevated	Exaggerated	L-thyroxin

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REVIEW OF LIETARTURE STUDIES

Almahmoud R et al (2024)⁹⁹ The Dubai Thalassaemia Centre evaluated the prevalence of diabetes mellitus, hypothyroidism, and growth retardation in children and adolescents with β -thalassemia major. The results showed that a considerable percentage of patients had decreased height velocity, making growth delay the most prevalent issue. Furthermore, some patients had increased TSH levels, which may indicate hypothyroidism, and 26.1% had pre-diabetes.

Oğuz SH et al (2023)¹⁰⁰ carried out a single-center cohort study with 103 adult betathalassemia patients. In thalassemic individuals, osteoporosis (37%) and hypogonadism (56%) were the most common endocrine consequences, while vitamin D deficiency was the most common endocrine problem (69%). Forty-two percent of the patients had three or more endocrine problems. Compared to patients without hypogonadism, those with the condition showed greater myocardial iron deposition ($P=.002$), lower haemoglobin concentrations ($P=.028$), and higher ferritin levels ($P=.014$). Additionally, there was a correlation between the second-hour glucose levels from the 75 g oral glucose tolerance test ($r=0.46$, $P=.001$) and the 5-year estimated mean ferritin levels and fasting plasma glucose ($r=0.29$, $P=.004$). Patients with diabetes (75% vs. 35%, $P=.027$) and hypogonadism (51% vs. 21%, $P=.003$) had higher rates of osteoporosis. However, neither the remaining endocrine issues nor their features were associated with thalassaemia. Osteoporosis and prediabetes/diabetes were the most prevalent endocrine-metabolic complications, occurring in 16% and 12% of patients, respectively, over the 3- and 5-year follow-up periods. They came to the conclusion that a sizable percentage of adult thalassemic patients experience several endocrine-metabolic issues. Regardless of ferritin levels, all thalassaemia major patients should have their risk of developing endocrine problems assessed.

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50 patients with Thalassaemia major participated in an observational research conducted by Nandini Dixit et al. (2022)¹⁰¹. They found that 16% had hypothyroidism, 10% had diabetes mellitus, 71.7% had delayed puberty, and 88% were low in stature. Ferritin levels were 3122 on average. Additionally, the study demonstrated that serum ferritin had a statistically significant negative link with serum calcium and a substantial positive correlation with serum TSH, fasting blood sugars, postprandial blood sugar, and delayed puberty. Serum ferritin and height did not significantly correlate.

Yadav SS et al (2022)¹⁰² We out a review to learn about the present prevalence of thalassaemia in various Indian regions and populations, as well as how to treat individuals with β -thalassemia major (β -TM) and β -thalassemia minor (β -thal). In Central India, the prevalence of β -thal trait varied from 1.4 to 3.4%, and among anaemia patients, 0.94% of them had β -TM. The prevalence of β -thal trait ranged from 8.50 to 37.90% in South India, while β -TM was found to range from 2.30 to 7.47%. The thalassemic burden was higher in the northern and western Indian states.

Tunç S et al (2022)¹⁰³ sought to identify the prevalence and distribution of endocrine issues in children and adolescents with a diagnosis of beta-thalassemia major, as well as to look into the connection between these complications and serum ferritin levels. Serum ferritin levels ranged from 562 to 10,251 ng/mL, with a median of 2,969 ng/mL. Eighty-three percent of the 48 participants in this study experienced at least one endocrine problem. Of them, 15 (31%) were younger than 10 years old. Short height (45%), osteopenia (34%), vitamin D deficiency (53%), pubertal disorder (mean 25% for each sex), and osteoporosis were the most prevalent endocrine problems. There was no correlation seen between ferritin levels and anthropometric, laboratory, or endocrine problems. They came to the conclusion that in order to enhance the quality of life

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for patients with thalassaemia major, it is critical to regularly evaluate growth, vitamin D status, puberty, and all other endocrine processes. Early detection and treatment of endocrine problems may improve these patients' quality of life and chances of survival.

Mahmoud R A and colleagues (2021)¹⁰⁴ have out research to identify endocrine abnormalities in young children with significant multitransfusion-transmitted thalassaemia. The most prevalent endocrine problems were thyroid conditions, with 11/120 (9.17%) patients having either subclinical or clinical hypothyroidism, and 9/120 (7.5%) patients having impaired glucose homeostasis. The study also demonstrated the strong correlation between elevated blood ferritin levels and poor drug compliance and a rise in endocrine illnesses. When compared to monotherapy, combined iron-chelating medications were linked to a lower frequency of endocrine problems.

In a cross-sectional investigation of more than 40 patients older than two years, **Karunaratna AMDS et al. (2020)**¹⁰⁵ found that pubertal delay was the most common endocrine consequence, accounting for 53% of the cases. Short stature, diabetes mellitus, and hypothyroidism were found to be 50%, 10%, 5%, and 2.5% prevalent, respectively. According to the study's findings, endocrine problems are widespread among patients with beta thalassaemia major and are associated with ageing.

Naresh Manne et al (2020)¹⁰⁶ One hundred and eight patients had endocrine problems. Twelve percent of patients had diabetes mellitus, thirty-six percent had hypothyroidism, and seventy-two percent had delayed puberty. In individuals with beta-thalassemia Major, the mean blood ferritin level was 5831.0 ± 2860.5 ng/ml, whereas in control subjects, it was within the normal range. They found that beta thalassaemia patients receiving frequent blood transfusion therapy had delayed puberty (72%), hypothyroidism (36%), and diabetes mellitus (12%). Since

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the serum ferritin level was significantly elevated in every study patient, they also discovered iron overload.

Mehran Karimi et al (2018)¹⁰⁷ The aim of this study is to determine the prevalence of endocrine complications in a large series of BTI patients. The survey included 721 BTI patients from 9 different countries. Osteoporosis (21.6%) and hypogonadism (12.6%) were the most common disease-related complications. Core hypothyroidism (8.3%), non-insulin-dependent diabetes mellitus (7.8%), primary hypothyroidism (5.5%), insulin-dependent diabetes mellitus (4.2%), hypoparathyroidism (2.2%), growth hormone deficiency (1.1%), adrenal mass (1%) and thyroid cancer (0.5%) were next in line.

A studied conducted by **M Delvecchio and L Cavallo (2010)**¹⁰⁸ shown that due to the absence of a growth spurt, disproportionately small stature is common and becomes more noticeable during adolescence. Because recombinant human growth hormone is unsuccessful for improving final height, they recommended long-term treatment. The study also demonstrated how the clinical spectrum of pubertal development includes everything from hypogonadism to a simple delay in the onset and progression of puberty, and how hormone replacement is required when puberty is absent or arrested. Additionally, the scientists discovered that autoimmune thyroiditis is nonexistent and central hypothyroidism is less common in these patients.

Farzad Najafipour et al (2008)¹⁰⁹ carried out research to assess endocrine abnormalities in patients older than 10 with beta-thalassemia major. The study demonstrated that the risk of secondary endocrine dysfunction persisted even after deferoxamine treatment was used to address iron overload. One of the most common endocrine problems was hypogonadism. Short stature, hypocalcaemia, impaired glucose tolerance, and overt and subclinical hypothyroidism are also common.

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Meropi toumba et al (2007)¹¹⁰ conducted a multicentric study in Cyprus with 435 patients. The study showed the prevalence of hypogonadotropic hypogonadism in 32.5%, short stature in 35%, acquired hypothyroidism in 5.9%, hypoparathyroidism in 1.2% and diabetes mellitus in 9.4% of patients. Delayed puberty and hypogonadism affects fertility, further affecting the quality of life of thalassemics.

In 3817 beta TM patients, a comprehensive international multicentric investigation by **De Sanctis V et al (2004)**¹¹¹ revealed that the prevalence of growth hormone insufficiency was 8.8% in females and 7.9% in males, and that short stature was observed in 31.1% of men and 30.5% of females. Hypoparathyroidism (6.9%), reduced glucose tolerance (6.5%), insulin-dependent diabetes mellitus (3.2%), and primary hypothyroidism (3.2%) were the most common endocrine complications, with lack of pubertal changes coming in first (40.5%). Serum liver enzymes were elevated in 65% of patients, and 51% of patients did not comply well with chelation therapy.

Aydinok Y et al (2002)¹¹² conducted a study to ascertain the prevalence and extent of endocrine problems in thirty-seven thalassaemia major (TM) patients. The average ferritin and haemoglobin levels were 3597 ± 1931 and 8.8 ± 0.6 , respectively. Forty percent of patients had development retardation, and one of the main causes of this condition was growth hormone insufficiency. In 47% of patients, gonadal dysfunction was found. 10.8% of patients had poor glucose metabolism, while 16% of patients had hypothyroidism.

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MATERIAL AND METHODS

- **Study design:** A prospective cohort study.
- **Study area:** Department of Pediatrics, Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka and Civil Hospital, Vijayapura, Karnataka, India.
- **Study period:** Research study was conducted from May 2023 to December 2024. Below is the work plan.

Table 1: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	% of allocation of study time	Duration in months
Understanding the problem, preparation of questionnaire.	5-10%	May 2023
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	May 2023 to June 2024
Analysis and interpretation	5-10%	July 2024 to December 2025
Dissertation write-up and submission	5-10%	January 2025

- **Sample size:** As per the study done In South India by Yadav SS et.al., the prevalence of β -thalassemia trait was between 8.50 and 37.90% and β -TM was reported to be between 2.30 and 7.47%. As per the study done by Toumba M et al., endocrine complications were seen in

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at least 35% patients. Taken into consideration the upper limit (7.47%) of above average prevalence of children with beta TM with endocrine complications in South India can be considered as 2.61%. Considering the confidence limit of these studies to be 95% with 5% level of significance and margin of error to be 0.05, the sample size was computed using the following formula:

$$\text{Sample size (n)} = (Z^2 * p * (1-p)) / d^2$$

Where,

z is the z score= 1.96

d is the margin of error= 0.05

n is the population size

p is the population proportion =2.61

The estimated sample size of this study is 39.

- **Sampling method:** Convenient sampling method
- **Inclusion criteria:**
 1. All patients of beta thalassemia major either admitted or paying an OPD visits within the age group of 1 to 18 years with more than 10 blood transfusions.
 2. Thalassemia patients willing for consent for the study.
- **Exclusion criteria:**
 1. All patients with alpha thalassemia, beta thalassemia minor and those with congenital endocrinopathies.

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METHODOLOGY:

Study Population:

The study included 51 patients with thalassemia major between the ages of 1 to 18 years. Patients were recruited from both outpatient departments and inpatient wards of the participating hospitals. The diagnosis of thalassemia major was confirmed through hemoglobin electrophoresis and clinical records.

Data Collection:

A comprehensive data collection approach was implemented using a structured proforma. Detailed demographic information was recorded, including age, sex, and residential address. The medical history focused on transfusion-related parameters, including the age at which transfusion was initiated and the total number of transfusions received. Information regarding iron chelation therapy was specifically documented.

Clinical Assessment:

For each participant, a comprehensive clinical evaluation was conducted. Using standardised methods, anthropometric measurements such as height, weight, and head circumference were taken. The conventional formula (weight in kg/height in m²) was used to determine the body mass index (BMI). Vital signs such as blood pressure, temperature, heart rate, and respiration rate were recorded. A comprehensive systemic examination was conducted, with particular attention to cardiovascular, respiratory, gastrointestinal, and central nervous systems. The presence and extent of hepatosplenomegaly were specifically noted.

Laboratory Investigations:

Blood samples were collected from all participants following standard protocols. Pre-transfusion hemoglobin levels were measured to assess the adequacy of transfusion therapy. A

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comprehensive endocrine evaluation was performed, which included:

- Thyroid function tests (T3, T4, TSH)
- Fasting blood sugar levels and post prandial blood sugar levels
- Serum ferritin levels to assess iron overload
- Serum calcium levels
- Gonadotropin levels (LH and FSH) in patients above 13 years of age

Pubertal Assessment:

For participants approaching or in the adolescent age group, pubertal development was assessed using Tanner staging. This evaluation was conducted with appropriate privacy and consent, with particular attention to signs of delayed puberty.

Quality Control:

All measurements and laboratory investigations were performed using standardized techniques and calibrated equipment. Laboratory tests were conducted in accredited laboratories with established quality control measures.

Data Management and Analysis:

Data was systematically recorded in the structured proforma and subsequently transferred to an electronic database for analysis. Appropriate statistical methods were employed to analyze the prevalence of various endocrine manifestations and their correlation with clinical parameters.

Ethical Considerations:

After receiving approval from the institutional ethics committee, the study was carried out. Parents or legal guardians gave their informed consent, and when appropriate, youngsters gave their assent. Throughout the duration of the trial, patient confidentiality was preserved.

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Follow-up Protocol:

Patients were followed up regularly during the study period to monitor the progression of endocrine manifestations and response to interventions. Any changes in clinical status or development of new endocrine complications were documented.

STATISTICAL ANALYSIS

SPSS version 21 was used to analyse the data after it was entered into an Excel sheet. The findings were displayed both graphically and tabularly. For quantitative data, the mean, median, standard deviation, and ranges were computed. Frequencies and percentages were used to express the qualitative data. The significance of the mean was tested using the student t test (two-tailed), and a P value of less than 0.05 was deemed significant.

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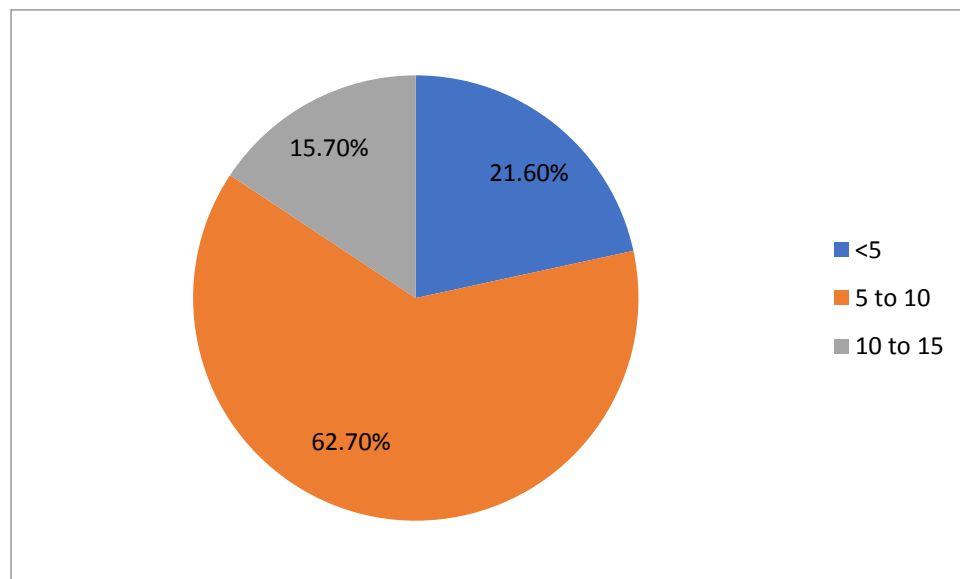
RESULTS

Table 1 and Graph 1 show the distribution of thalassemic children according to age. The majority of patients (62.7%) were in the 5-10 years age group, followed by those under 5 years (21.6%), and the smallest group was 10-15 years (15.7%). This indicates that the study primarily included young children with thalassemia major.

Table 1: Distribution of thalassemic children according to age(n=51)

Age (in years)	Frequency	Percentage
<5	11	21.6%
5-10	32	62.7%
10-15	8	15.7%
Total	51	100%

Graph 1: Distribution of thalassemic children according to age



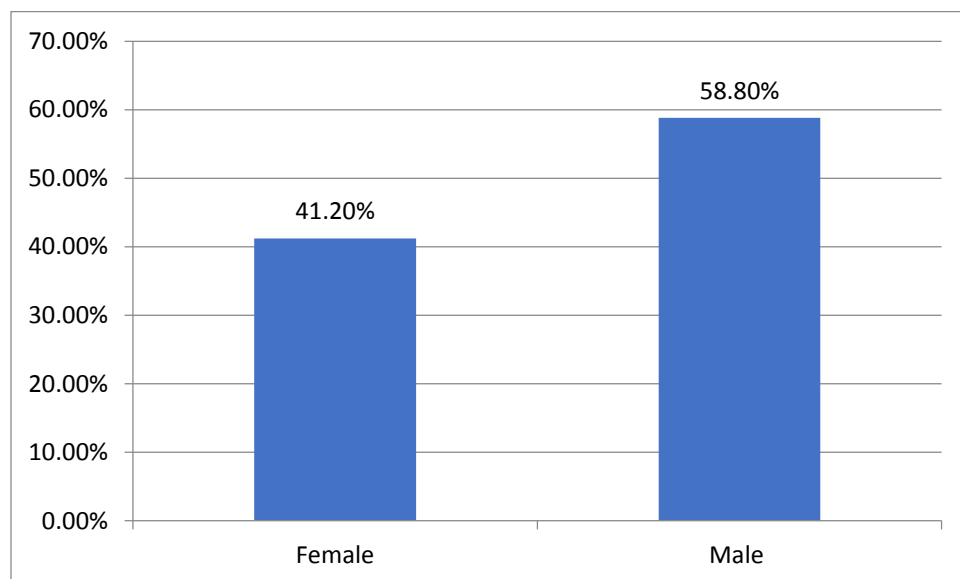
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Table 2 and Graph 2 show the distribution of thalassemic children according to gender. There were more male patients (58.8%) compared to female patients (41.2%) in the study population, with a total of 51 patients.

Table 2: Distribution of thalassemic children according to gender(n=51)

Gender	Frequency	Percentage
Female	21	41.2%
Male	30	58.8%
Total	51	100%

Graph 2: Distribution of thalassemic children according to gender



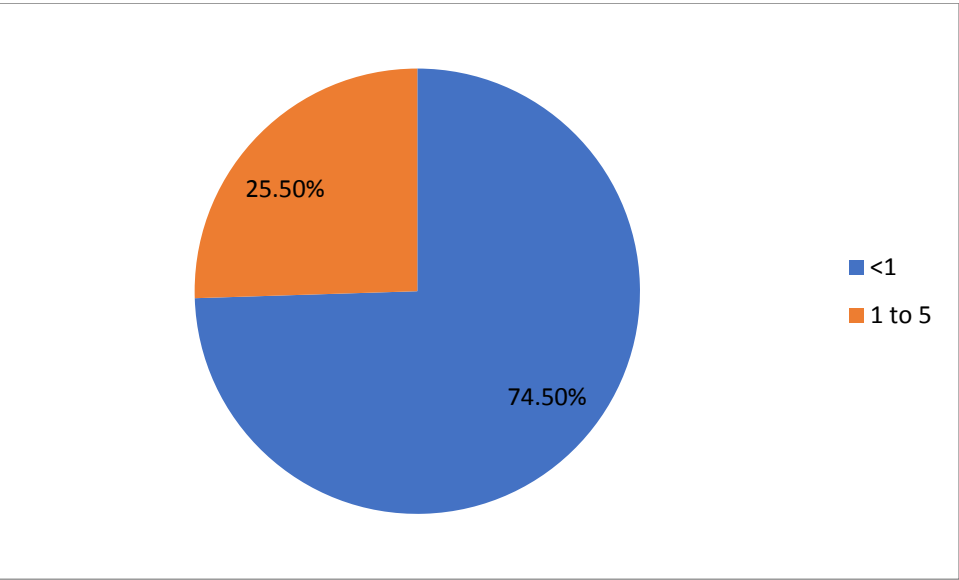
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Table 3 and Graph 3 show the distribution of thalassemic children according to age of starting transfusion. The majority of patients (74.5%) started receiving blood transfusions before the age of 1 year, while the remaining (25.5%) started between 1-5 years. This suggests early diagnosis and treatment initiation in most cases.

Table 3: Distribution of thalassemic children according to age of starting transfusion(n=51)

Age of starting transfusion (years)	Frequency	Percentage
<1	38	74.5%
1-5	13	25.5%
Total	51	100%

Graph 3: Distribution of thalassemic children according to age of starting transfusion



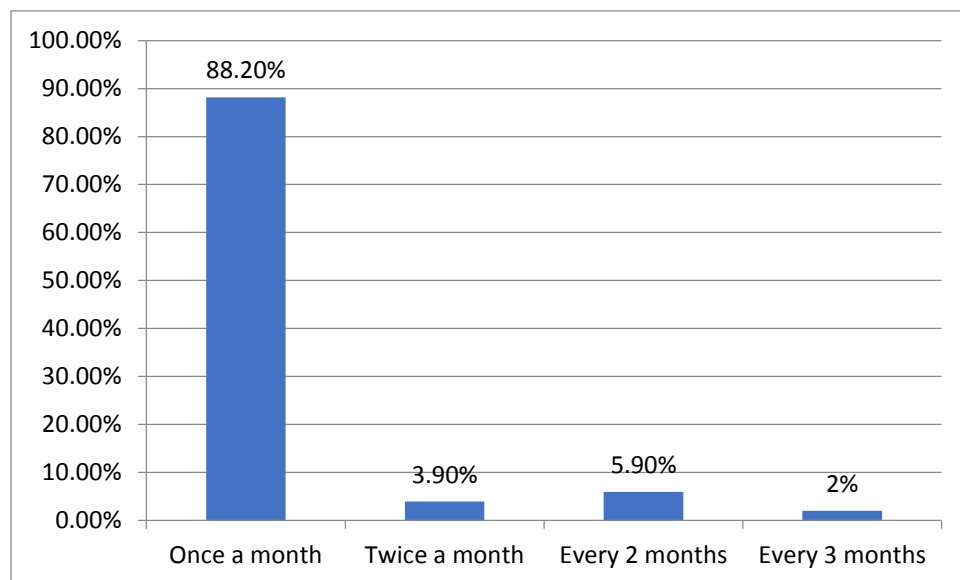
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Table 4 and Graph 4 show the distribution of thalassemic children according to frequency of transfusion. Most patients (88.2%) received transfusions once a month, with smaller percentages receiving transfusions at different intervals: twice a month (3.9%), every 2 months (5.9%), or every 3 months (2%).

Table 4: Distribution of thalassemic children according to frequency of transfusion(n=51)

Frequency of transfusion	Frequency	Percentage
Twice a month	2	3.9%
Once a month	45	88.2%
Every 2 months	3	5.9%
Every 3 months	1	2%
Total	51	100%

Graph 4: Distribution of thalassemic children according to frequency of transfusion



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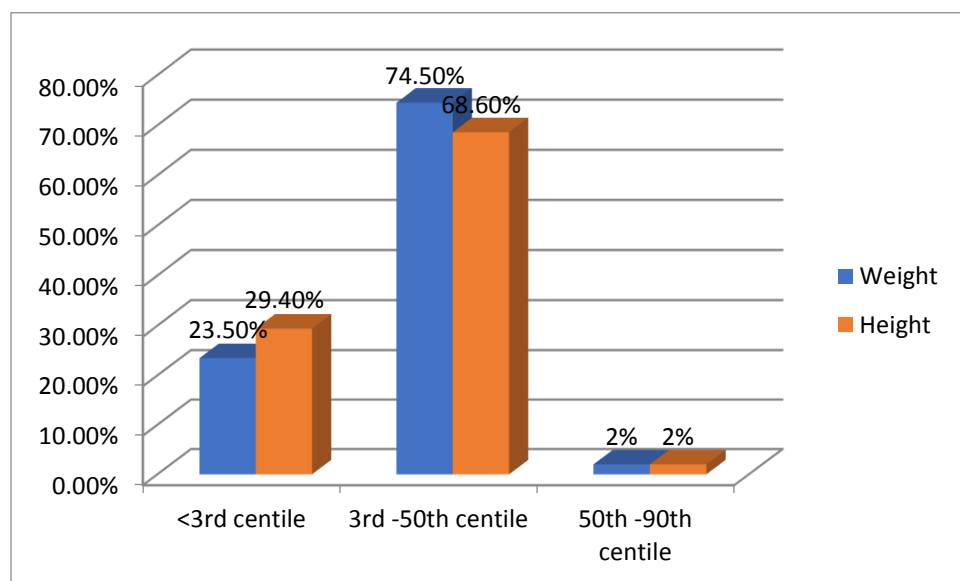
Table 5 and Graph 5 show the distribution of thalassemic children according to anthropometry.

For weight, 23.5% of patients were below the 3rd centile, 74.5% were between the 3rd-50th centile, and only 2% were in the 50th-90th centile. For height, 29.4% were below the 3rd centile, 68.6% were between the 3rd-50th centile, and 2% were in the 50th-90th centile. This shows growth retardation is common in these patients.

Table 5: Distribution of thalassemic children according to anthropometry(n=51)

Anthropometry	Weight	Height
<3rd centile	12 (23.5%)	15 (29.4%)
3rd -50th centile	38 (74.5%)	35 (68.6%)
50th -90th centile	1 (2%)	1 (2%)

Graph 5: Distribution of thalassemic children according to anthropometry



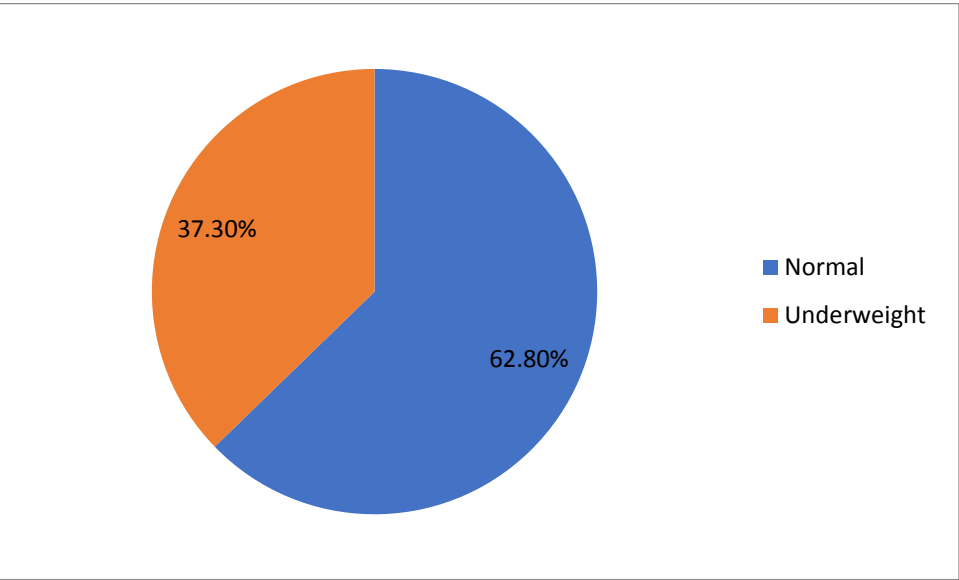
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Table 6 and Graph 6 show the distribution of thalassemic children according to BMI. Most patients (62.8%) had normal BMI, while 37.3% were underweight. No patients were classified as overweight or obese.

Table 6: Distribution of thalassemic children according to BMI(n=51)

BMI	Frequency	Percentage
Normal	32	62.8%
Underweight	19	37.3%
Total	51	100%

Graph 6: Distribution of thalassemic children according to BMI



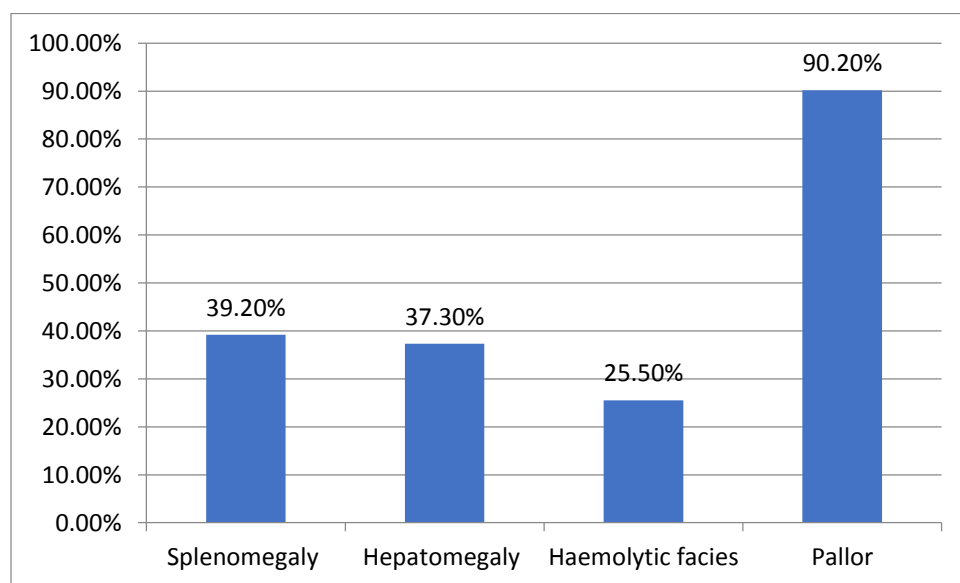
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Table 7 and Graph 7 show the distribution of thalassemic children according to clinical presentation. Pallor was the most common clinical finding (90.2%), followed by splenomegaly (39.2%), hepatomegaly (37.3%), and hemolytic facies (25.5%).

Table 7: Distribution of thalassemic children according to clinical presentation(n=51)

clinical presentation	Frequency	Percentage
Splenomegaly	20	39.2%
Hepatomegaly	19	37.3%
Haemolytic facies	13	25.5%
Pallor	46	90.2%

Graph 7: Distribution of thalassemic children according to clinical presentation



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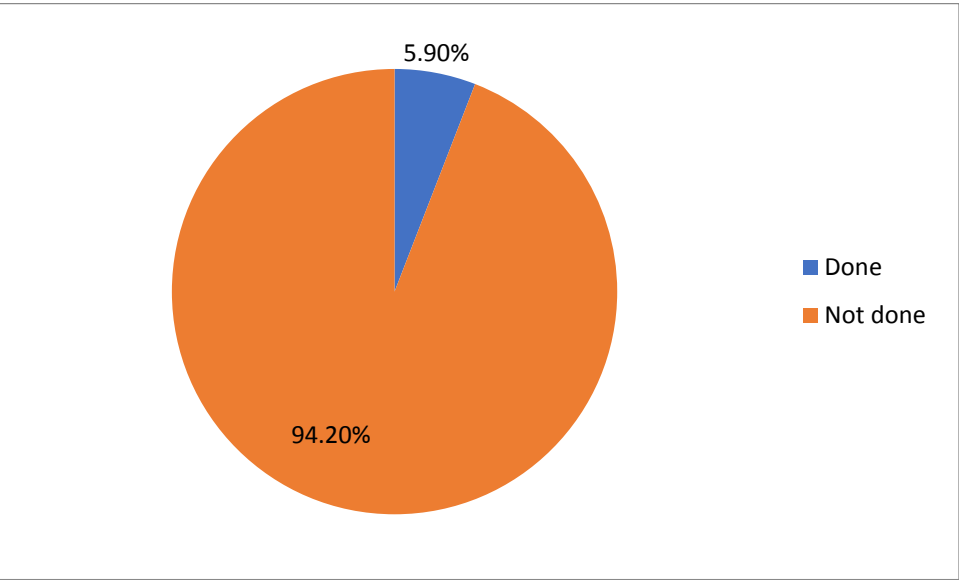
Table 8 and Graph 8 show the distribution of thalassemic children according to splenectomy.

Only 5.9% of patients had undergone splenectomy, while the majority (94.2%) had not had this procedure.

Table 8: Distribution of thalassemic children according to splenectomy(n=51)

Splenectomy	Frequency	Percentage
Done	3	5.90%
Not done	48	94.20%
Total	51	100%

Graph 8: Distribution of thalassemic children according to splenectomy



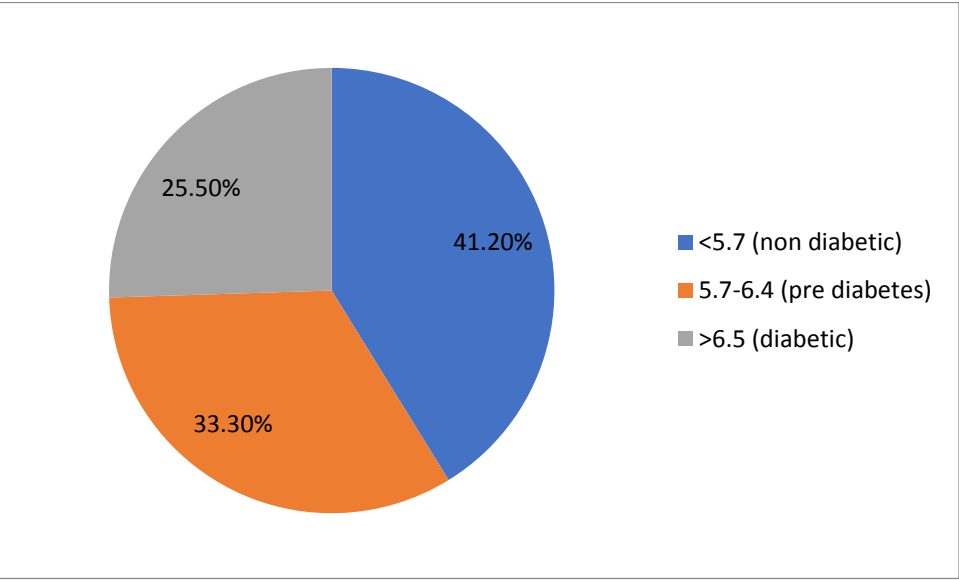
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Table 9 and Graph 9 show the distribution of thalassemic children according to HbA1c. 41.2% had normal levels (<5.7%), 33.3% had prediabetic levels (5.7-6.4%), and 25.5% had diabetic levels (>6.5%), indicating a high prevalence of glucose metabolism disorders.

Table 9: Distribution of thalassemic children according to HbA1c(n=51)

HbA1c	Frequency	Percentage
<5.7 (non diabetic)	21	41.2%
5.7-6.4 (pre diabetes)	17	33.3%
>6.5 (diabetic)	13	25.5%
Total	51	100%

Graph 9: Distribution of thalassemic children according to HbA1c



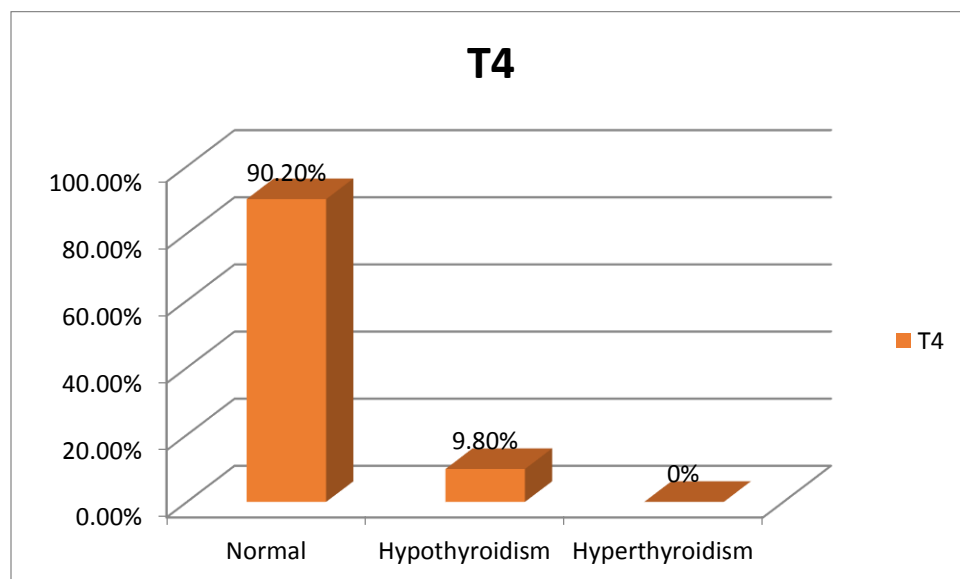
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Table 10 and Graph 10 show the distribution of thalassemic children according to T4 thyroid hormone levels. For T4, 90.2% had normal levels and 9.8% had hypothyroidism. No patients presented with hyperthyroidism.

Table 10: Distribution of thalassemic children according to T4(n=51)

Thyroid function tests	T4
Normal	46 (90.2%)
Hypothyroidism	5 (9.8%)
Hyperthyroidism	-

Graph 10: Distribution of thalassemic children according to T4



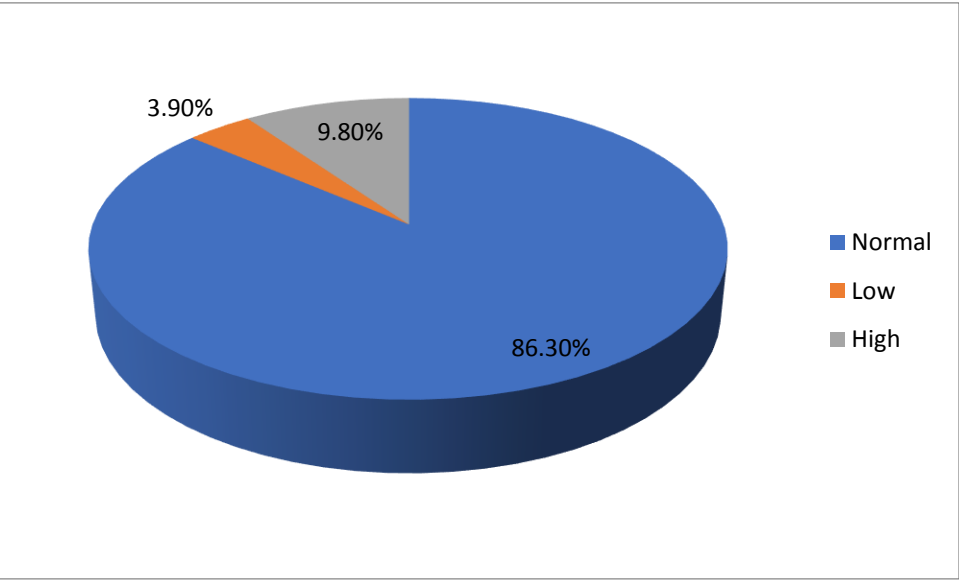
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Table 11 and Graph 11 show the distribution of thalassemic children s according to TSH. Most patients (86.3%) had normal TSH levels, while 9.8% had high levels and 3.9% had low levels.

Table 11: Distribution of thalassemic children according to TSH (n=51)

TSH	Frequency	Percentage
Normal	44	86.3%
Low	2	3.9%
High	5	9.8%
Total	51	100%

Graph 11: Distribution of thalassemic children according to TSH



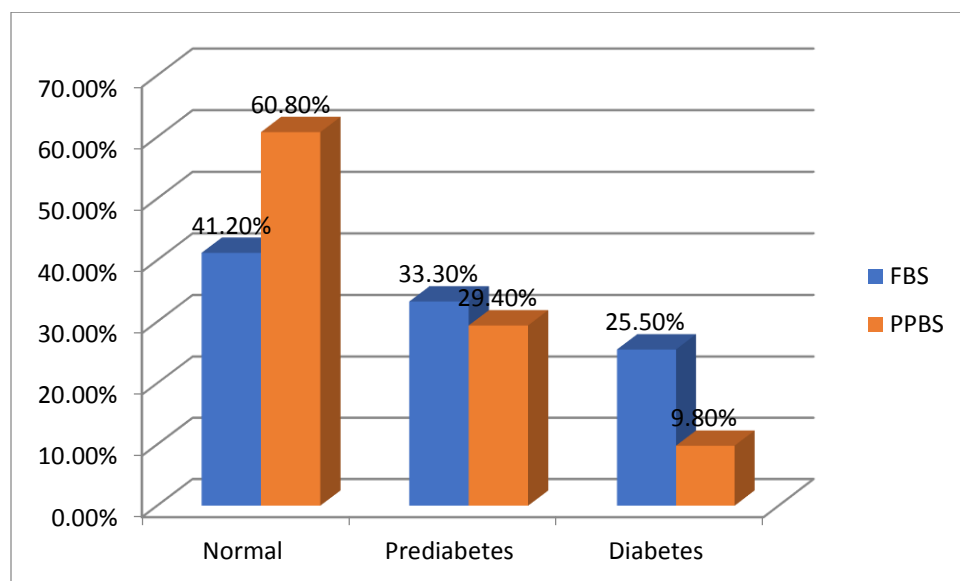
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Table 12 and Graph 12 show the distribution of thalassemic children according to fasting blood sugar (FBS) and postprandial blood sugar (PPBS). For FBS, 41.2% had normal levels, 33.3% had prediabetic levels, and 25.5% had diabetic levels. For PPBS, 60.8% had normal levels, 29.4% had prediabetic levels, and 9.8% had diabetic levels.

Table 12: Distribution of thalassemic children according to FBS and PPBS (n=51)

Parameters	FBS	PPBS
Normal	21 (41.2%)	31 (60.8%)
Prediabetes	17 (33.3%)	15 (29.4%)
Diabetes	13 (25.5%)	5 (9.8%)

Graph 12: Distribution of thalassemic children according to FBS and PPBS



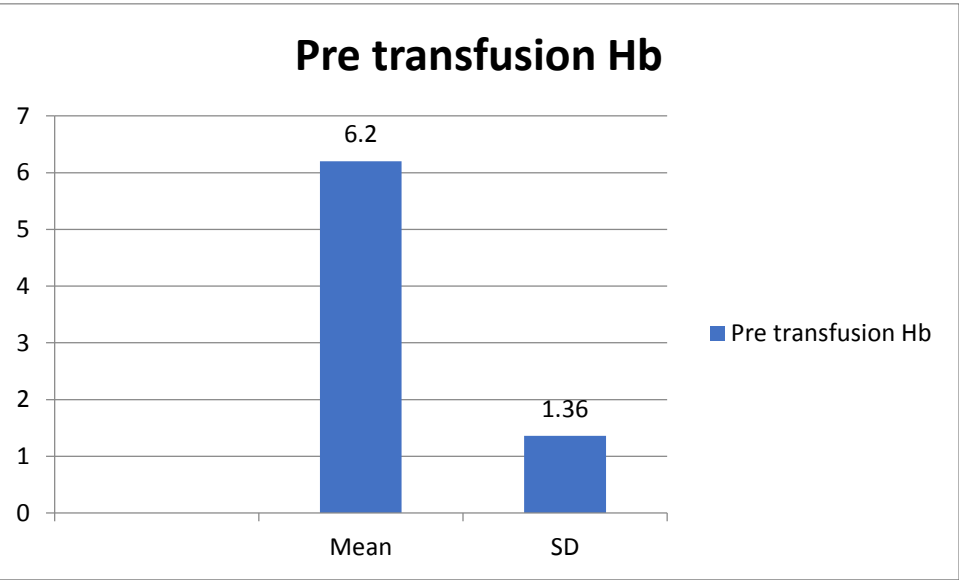
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Table 13 and Graph 13 show the distribution of thalassemic children according to pre-transfusion hemoglobin. The mean pre-transfusion Hb was 6.2±1.36 g/dL, indicating severe anemia before transfusions.

Table 13: Distribution of thalassemic children according to Pre transfusion Hb (n=51)

Parameters	Pre transfusion Hb
Mean±SD	6.2±1.36

Graph 13: Distribution of thalassemic children according to Pre transfusion Hb



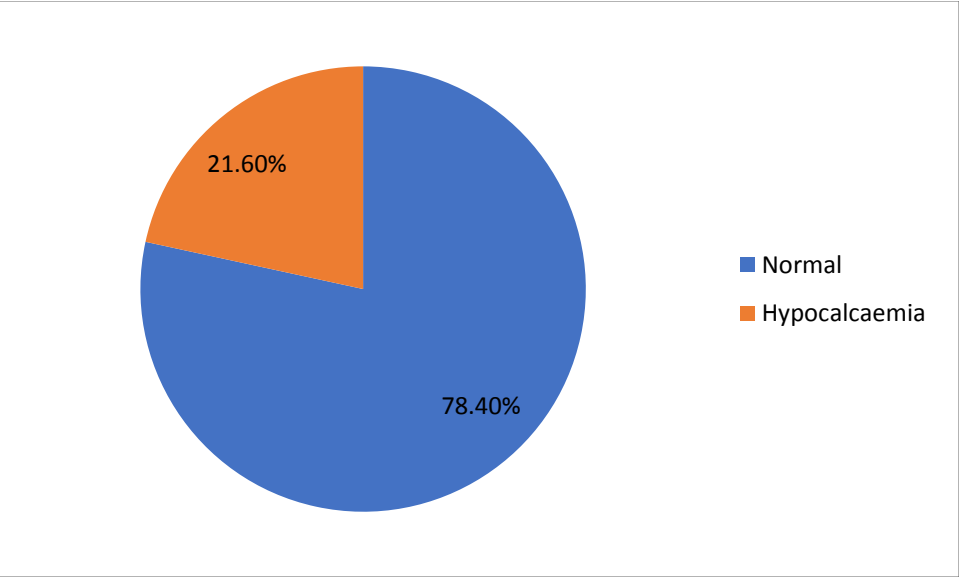
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Table 14 and Graph 14 show the distribution of thalassemic children according to calcium levels. Most patients (78.4%) had normal calcium levels, while 21.6% had hypocalcemia.

Table 14: Distribution of thalassemic children according to calcium(n=51)

Calcium	Frequency	Percentage
Normal	39	78.4%
Hypocalcaemia	11	21.6%
Total	51	100%

Graph 14: Distribution of thalassemic children according to calcium



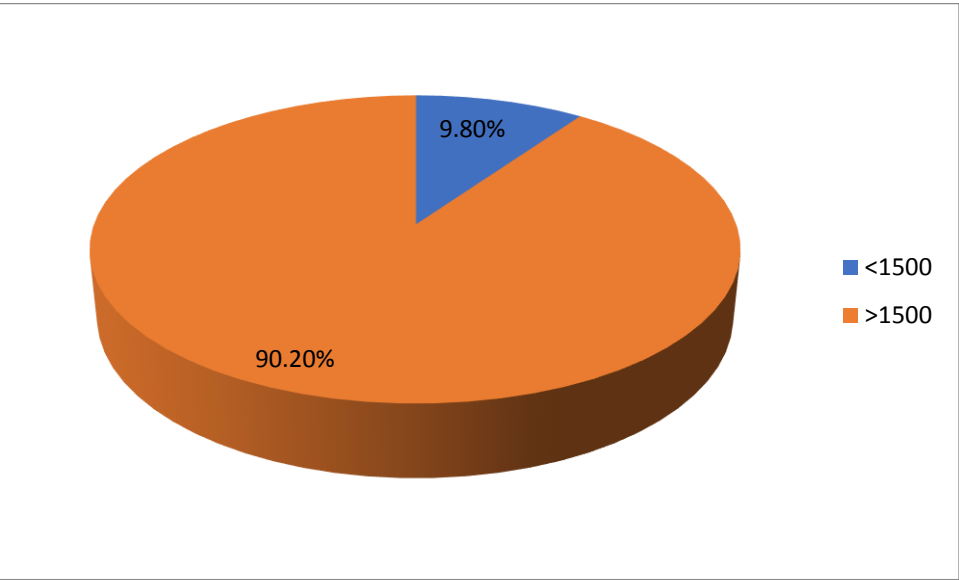
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Table 15 and Graph 15 show the distribution of thalassemic children according to serum ferritin. The vast majority (90.2%) had ferritin levels >1500 ng/mL, indicating significant iron overload, while only 9.8% had levels <1500 ng/mL.

Table 15: Distribution of thalassemic children according to serum ferritin(n=51)

Serum ferritin	Frequency	Percentage
<1500	5	9.8%
>1500	46	90.2%
Total	51	100%

Graph 15: Distribution of thalassemic children according to serum ferritin



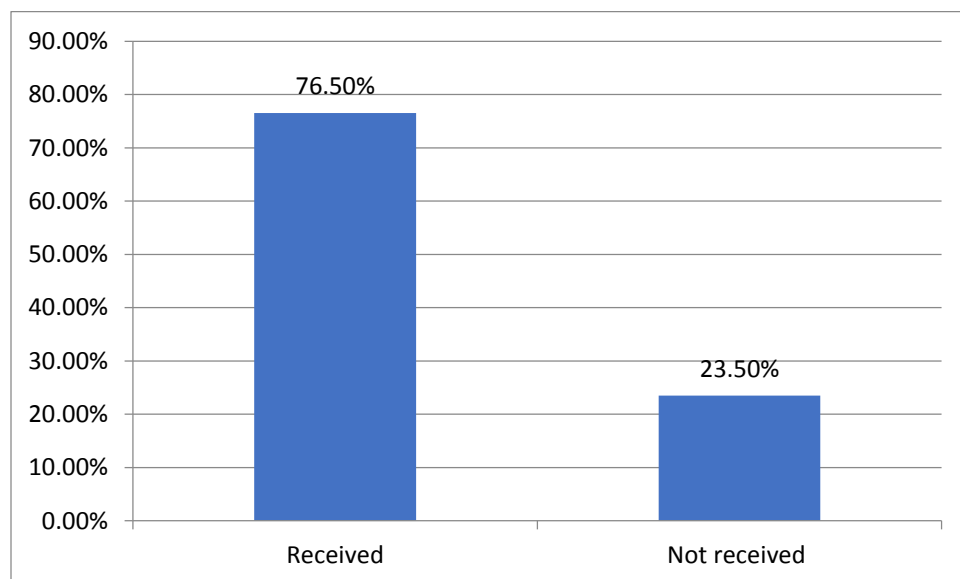
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Table 16 and Graph 16 show the distribution of thalassemic children according to iron chelation therapy. Most patients (76.5%) received chelation therapy, while 23.5% did not receive this treatment.

Table 16: Distribution of thalassemic children according to iron chelation(n=51)

Iron chelation	Frequency	Percentage
Received	39	76.5%
Not received	12	23.5%
Total	51	100%

Graph 16: Distribution of thalassemic children according to iron chelation



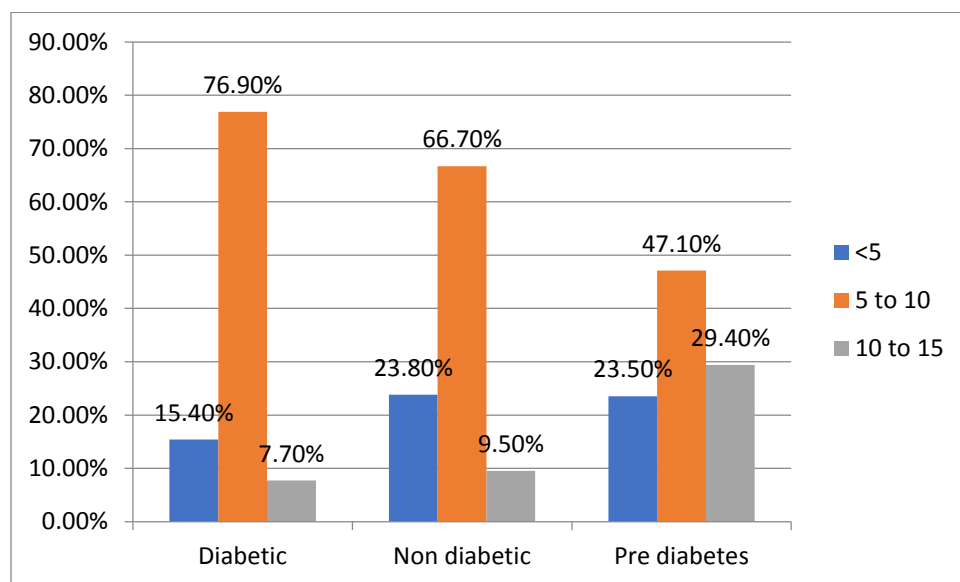
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Table 17 and graph 17 shows the association of HbA1c with age. There was no statistically significant association ($p=0.33$) between age groups and HbA1c categories, though diabetic HbA1c levels were most common in the 5-10 years age group (76.9%).

Table 17: Association of HbA1c with age(n=51)

Age (in years)	HbA1c			p-value
	Diabetic	Non diabetic	Pre diabetes	
<5	2 (15.4%)	5 (23.8%)	4 (23.5%)	0.33
5-10	10 (76.9%)	14 (66.7%)	8 (47.1%)	
10-15	1 (7.7%)	2 (9.5%)	5 (29.4%)	
Total	13 (100%)	21 (100%)	17 (100%)	

Graph 17: Association of HbA1c with age



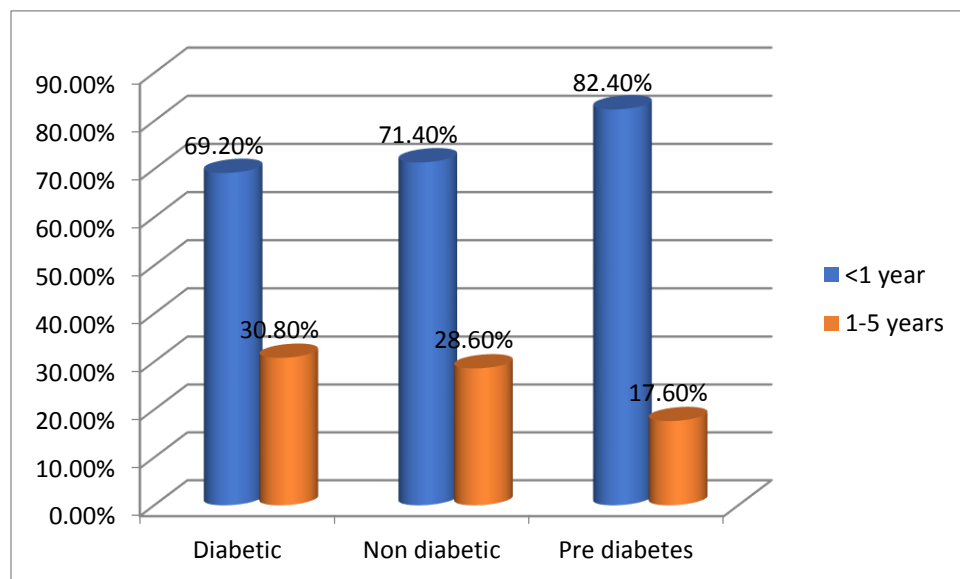
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Table 18 shows the association of HbA1c with age of starting transfusion. There was no significant association ($p=0.65$) between when transfusions started and HbA1c status.

Table 18: Association of HbA1c with age of starting transfusion(n=51)

age of starting transfusion	HbA1c			p-value
	Diabetic	Non diabetic	Pre diabetes	
<1 year	9 (69.2%)	15 (71.4%)	14(82.4%)	0.65
1-5 years	4 (30.8%)	6 (28.6%)	3 (17.6%)	
Total	13(100%)	21 (100%)	17 (100%)	

Graph 18: Association of HbA1c with age of starting transfusion



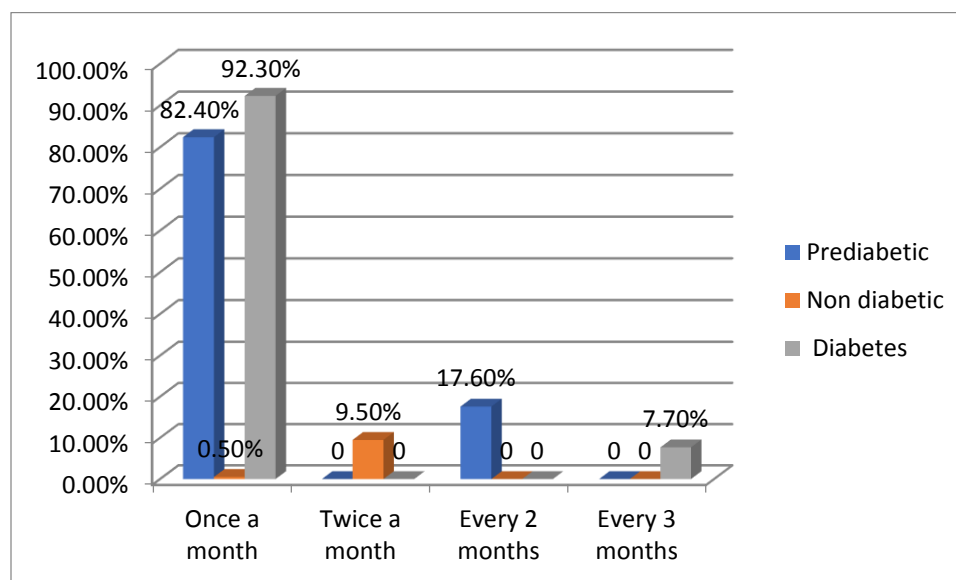
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Table 19 and graph 19 shows the association of HbA1c with frequency of transfusion. There was no statistically significant association ($p=0.06$) between transfusion frequency and HbA1c categories.

Table 19: Association of HbA1c with frequency of transfusion(n=51)

frequency of transfusion	HbA1c			p-value
	Prediabetic	Non diabetic	Diabetes	
Once a month	14 (82.4%)	19 (0.5%)	12 (92.3%)	0.06
Twice a month	0	2 (9.5%)	0	
Every 2 months	3 (17.6%)	0	0	
Every 3 months	0	0	1 (7.7%)	
Total	17(100%)	21 (100%)	13 (100%)	

Graph 19: Association of HbA1c with frequency of transfusion



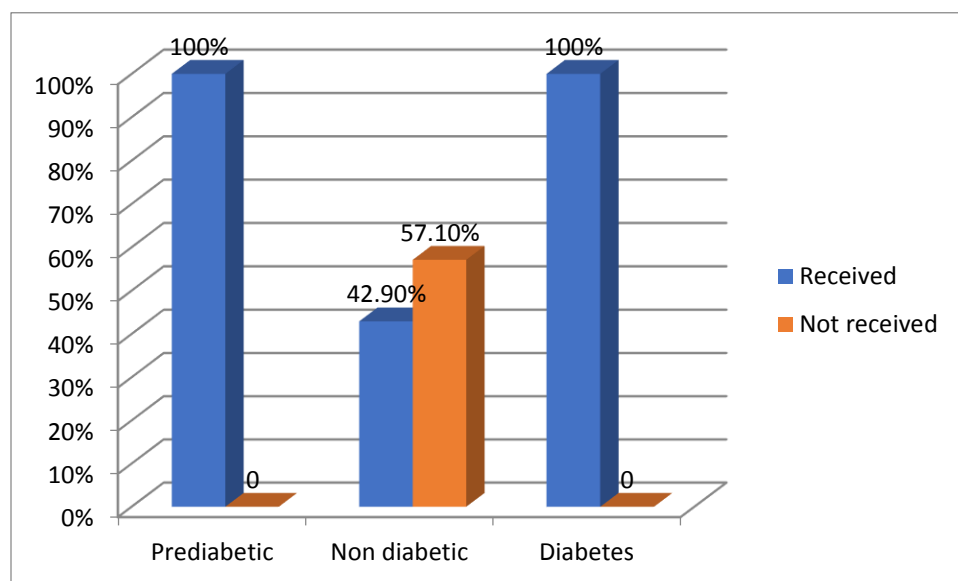
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Table 20 and graph 20 shows the association of HbA1c with chelation therapy. There was a highly significant association ($p < 0.001$) between receiving chelation therapy and HbA1c status. All prediabetic and diabetic patients received chelation therapy, suggesting a possible relationship between iron chelation and glucose metabolism.

Table 20: Association of HbA1c with chelation therapy(n=51)

Chelation therapy	HbA1c			p-value
	Prediabetic	Non diabetic	Diabetes	
Received	17 (100%)	9 (42.9%)	13 (100%)	<0.001
Not received	0	12 (57.1%)	0	
Total	17 (100%)	21 (100%)	13 (100%)	

Graph 20: Association of HbA1c with chelation therapy



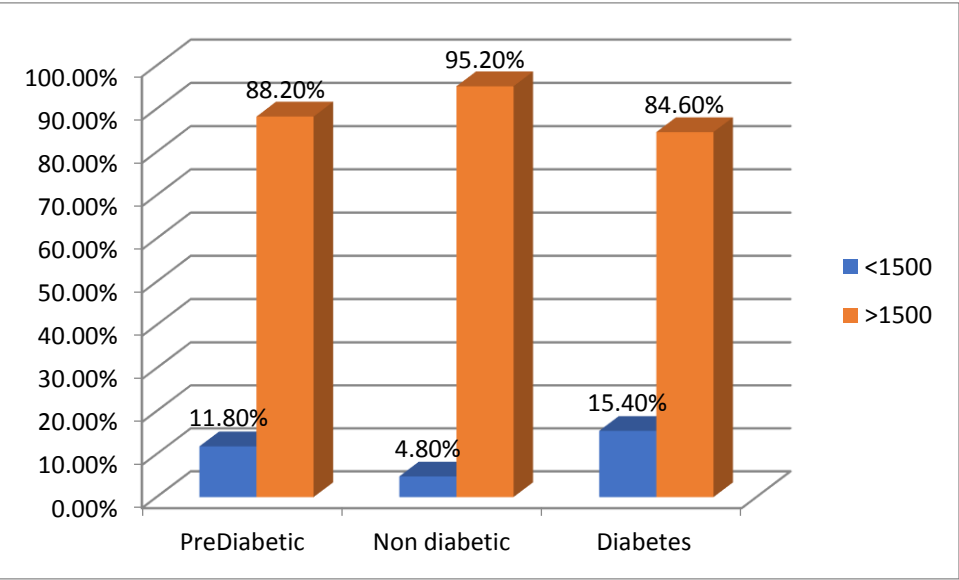
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Table 21 and graph 21 shows the association of HbA1c with serum ferritin levels. There was no significant association ($p=0.56$) between ferritin levels and HbA1c categories.

Table 21: Association of HbA1c with serum ferritin levels(n=51)

serum ferritin levels	HbA1c			p-value
	PreDiabetic	Non diabetic	Diabetes	
<1500	2 (11.8%)	1 (4.8%)	2 (15.4%)	0.56
>1500	15 (88.2%)	20 (95.2%)	11 (84.6%)	
Total	17 (100%)	21 (100%)	13 (100%)	

Graph 21: Association of HbA1c with serum ferritin levels



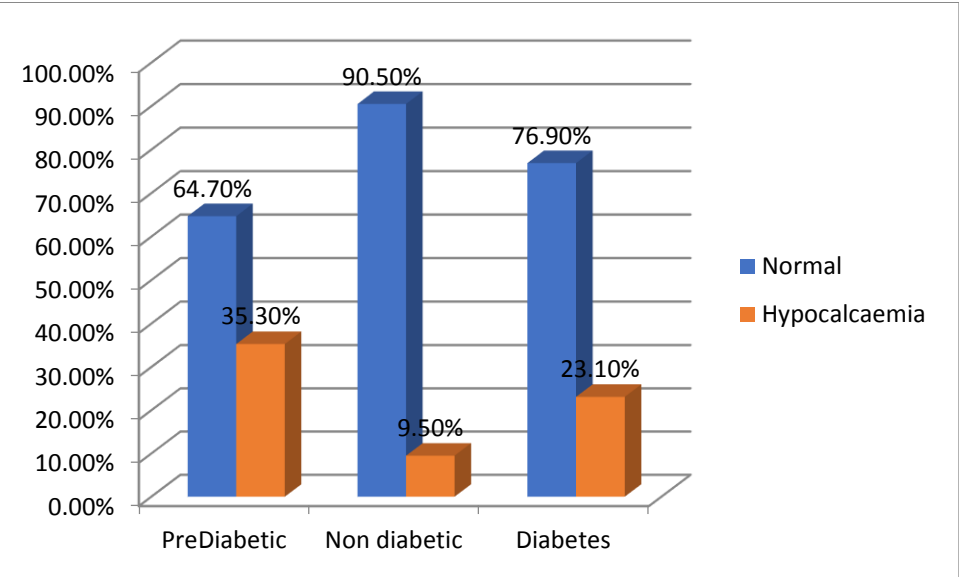
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Table 22 and graph 22 shows the association of HbA1c with calcium levels. There was no significant association ($p=0.19$) between calcium levels and HbA1c categories.

Table 22: Association of HbA1c with calcium levels(n=51)

Calcium levels	HbA1c			p-value
	PreDiabetic	Non diabetic	Diabetes	
Normal	11 (64.7%)	19 (90.5%)	10 (76.9%)	0.19
Hypocalcaemia	6 (35.3%)	2 (9.5%)	3 (23.1%)	
Total	17 (100%)	21 (100%)	13 (100%)	

Graph 22: Association of HbA1c with calcium levels



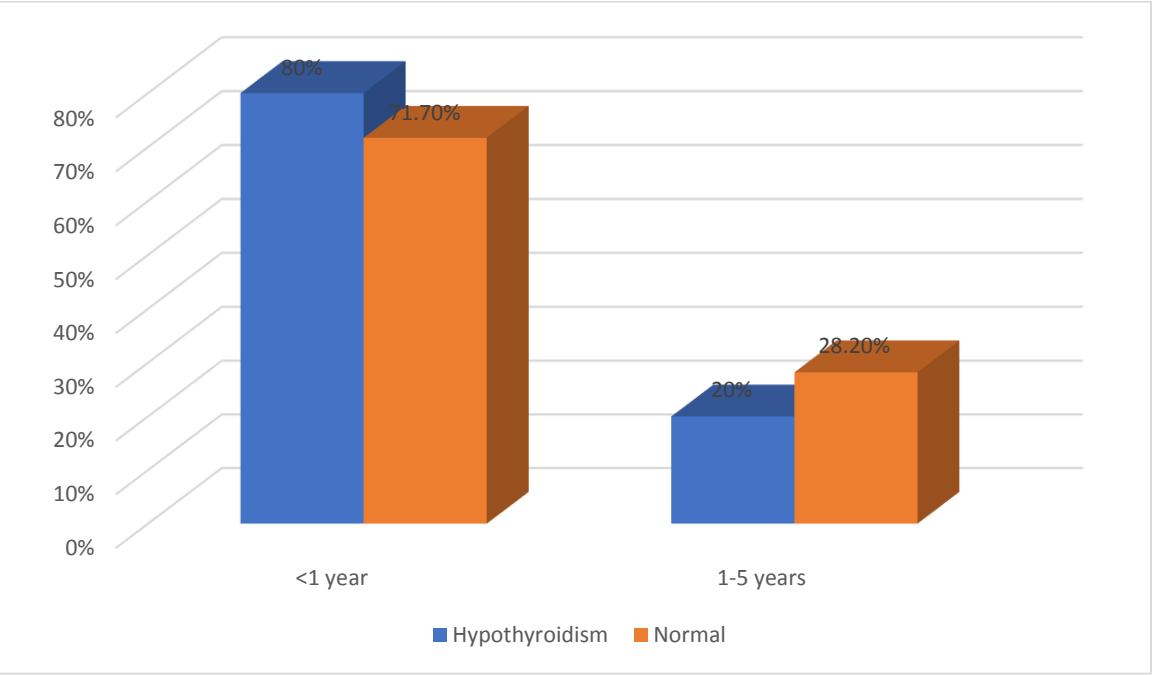
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Table 23 and graph 23 shows the association of thyroid disorder with age of starting transfusion. There was no significant association (p=0.69) between when transfusions started and thyroid function.

Table 23: Association of thyroid disorder with age of starting transfusion(n=51)

age of starting transfusion	Thyroid disorder		p-value
	Hypothyroidism	Normal	
<1 year	4 (80%)	33 (71.7%)	0.69
1-5 years	1 (20%)	13 (28.2%)	
Total	5 (100%)	46(100%)	

Graph 23: Association of thyroid disorder with age of starting transfusion



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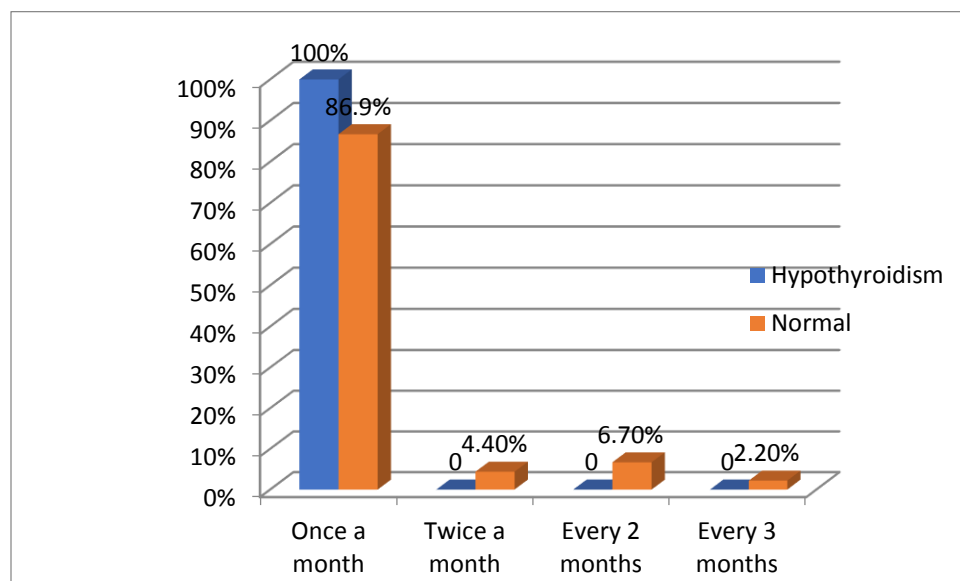
Table 24 and graph 24 shows the association of thyroid disorder with frequency of transfusion.

There was no significant association ($p=0.86$) between transfusion frequency and thyroid function.

Table 24: Association of Thyroid disorder with frequency of transfusion(n=51)

frequency of transfusion	Thyroid disorder		p-value
	Hypothyroidism	Normal	
Once a month	5 (100%)	40 (86.9%)	0.86
Twice a month	0	2 (4.4%)	
Every 2 months	0	3 (6.7%)	
Every 3 months	0	1 (2.2%)	
Total	5 (100%)	46 (100%)	

Graph 24: Association of Thyroid disorder with frequency of transfusion



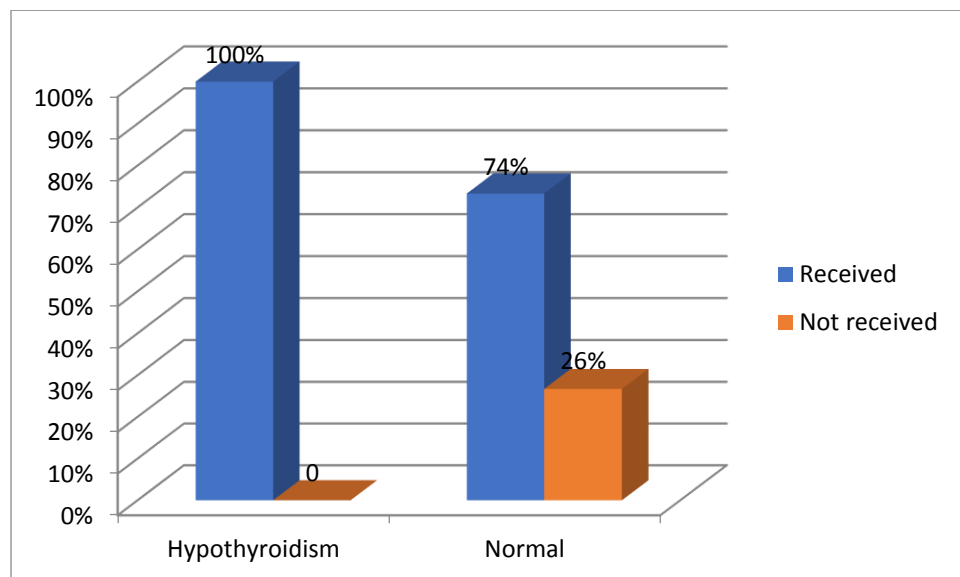
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Table 25 and graph 25 shows the association of thyroid disorder with chelation therapy. There was no significant association ($p=0.19$) between chelation therapy and thyroid function, though all hypothyroid patients received chelation therapy.

Table 25: Association of Thyroid disorder with chelation therapy(n=51)

chelation therapy	Thyroid disorder		p-value
	Hypothyroidism	Normal	
Received	5 (100%)	34 (74%)	0.19
Not received	0	12 (26%)	
Total	5 (100%)	46 (100%)	

Graph 25: Association of Thyroid disorder with chelation therapy



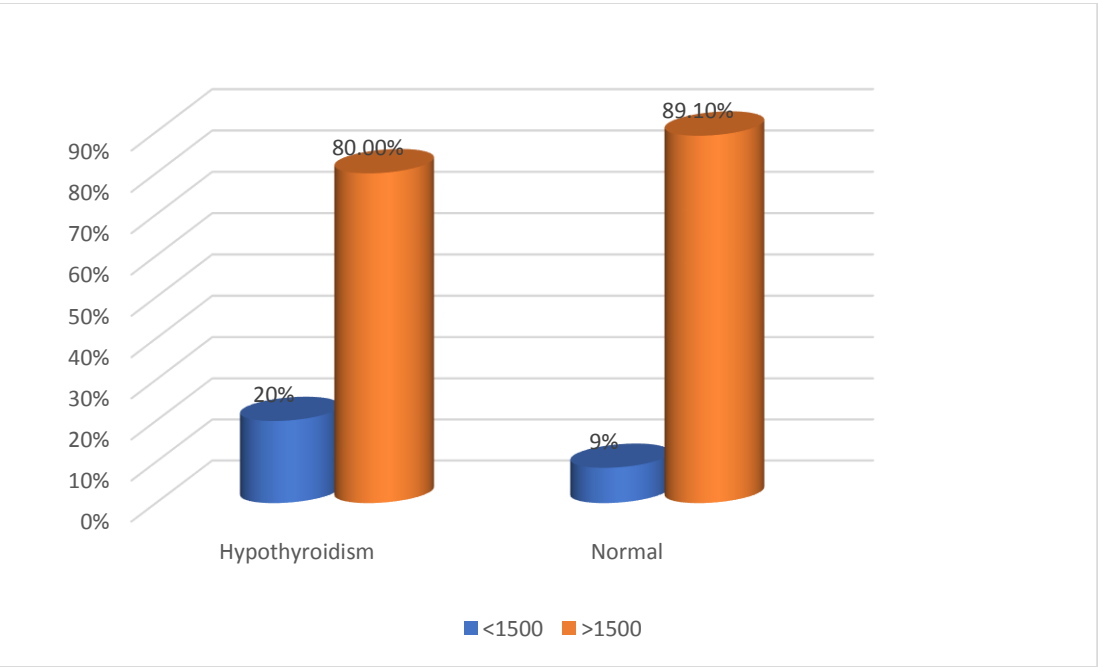
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Table 26 and graph 26 shows the association of thyroid disorder with serum ferritin levels. There was no significant association ($p=0.43$) between ferritin levels and thyroid function.

Table 26: Association of Thyroid disorder with serum ferritin levels(n=51)

serum ferritin levels	Thyroid disorder		p-value
	Hypothyroidism	Normal	
<1500	1 (20%)	4 (8.6%)	0.43
>1500	4 (80%)	41 (89.1%)	
Total	5 (100%)	46 (100%)	

Graph 26: Association of Thyroid disorder with serum ferritin levels



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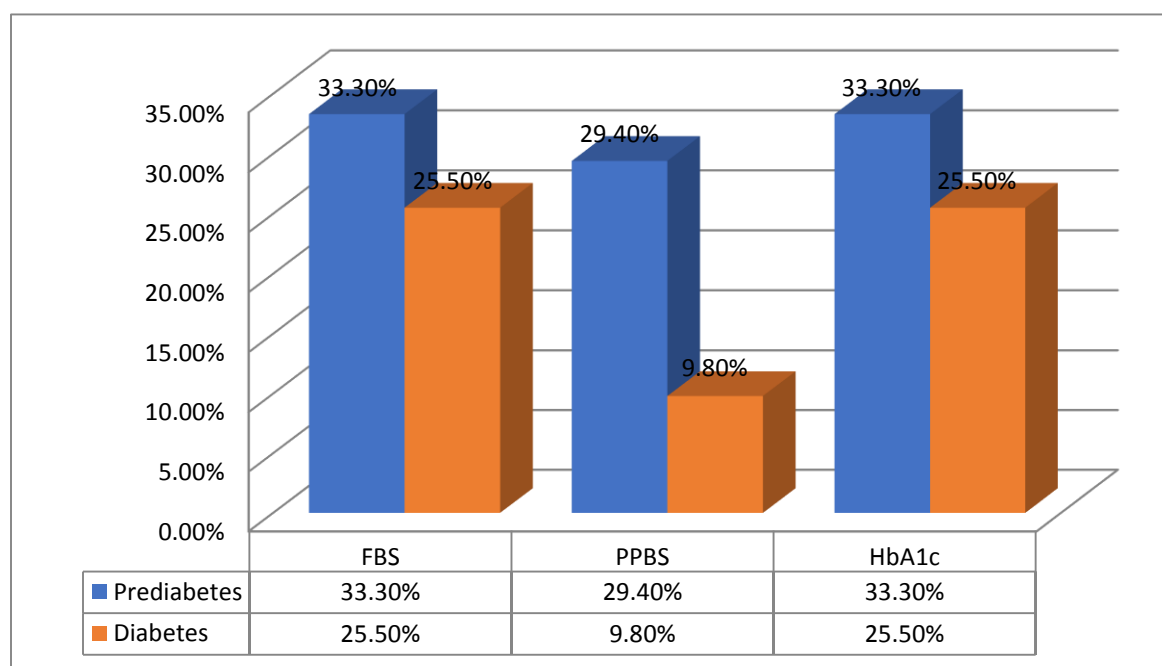
Table 27 and graph 27 shows the distribution of patients according to high blood sugar levels.

Prediabetes was identified in 33.3% of patients using FBS, 29.4% using PPBS, and 33.3% using HbA1c. Diabetes was identified in 25.5% using FBS, 9.8% using PPBS, and 25.5% using HbA1c.

Table 27: Distribution of patients according to high blood sugar levels(n=51)

Blood sugar levels	FBS	PPBS	HbA1c
Prediabetes	17 (33.3%)	15 (29.4%)	17 (33.3%)
Diabetes	13(25.5%)	5 (9.8%)	13 (25.5%)

Graph 27: Distribution of patients according to high blood sugar levels



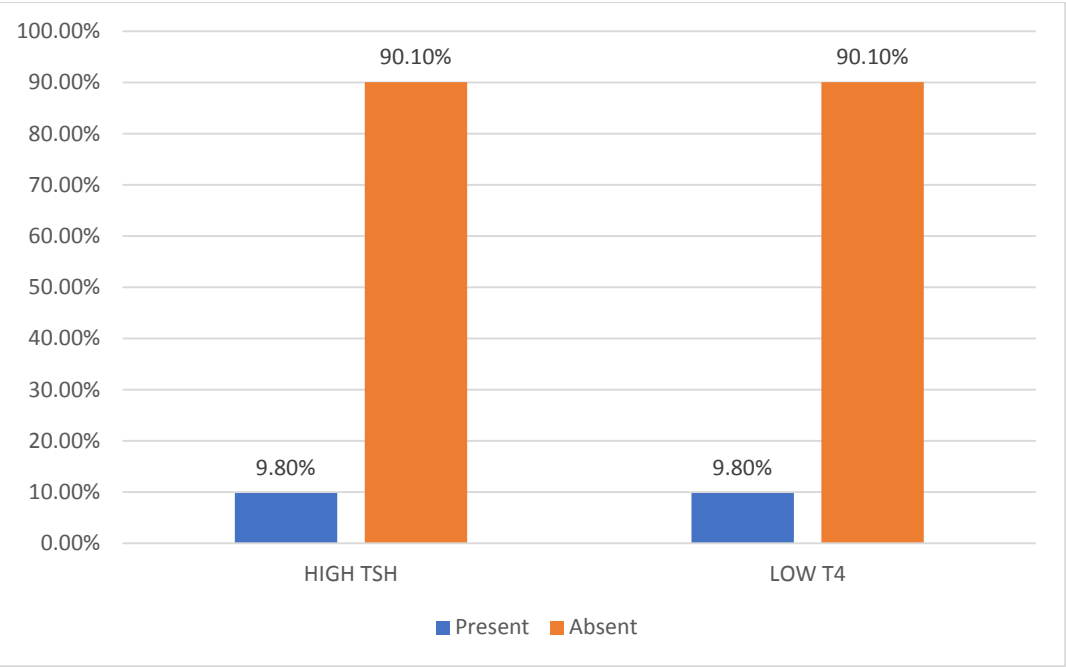
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Table 28 and graph 28 shows the distribution of patients according to hypothyroidism. 9.8% of patients had hypothyroidism as indicated by both low TSH and high T4 levels.

Table 28: Distribution of patients according to hypothyroidism(n=51)

Hypothyroidism	HIGH TSH	LOW T4
Present	5 (9.8%)	5 (9.8%)
Absent	46 (90.1%)	46 (90.1%)

Graph 28: Distribution of patients according to hypothyroidism



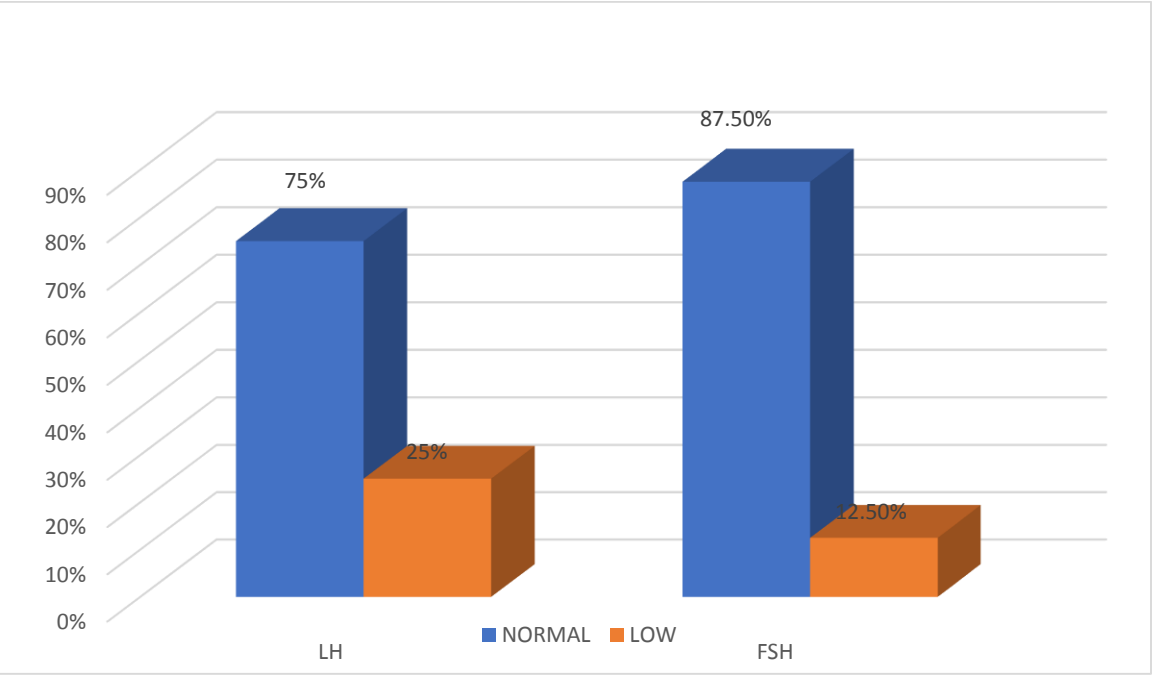
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Table 29 and Graph 29 show the distribution of patients (age >13 years, n=8) according to LH and FSH gonadotropin levels. For LH, 75% had normal levels and 25% had low levels. For FSH, 87.5% had normal levels and 12.5% had low levels.

Table 29: Distribution of patients (age > 13 years, n=8) according to LH and FSH

Gonadotrophins	LH	FSH
Normal	6(75%)	7(87.5%)
Low	2 (25%)	1 (12.5%)

Graph 29: Distribution of patients according to LH and FSH



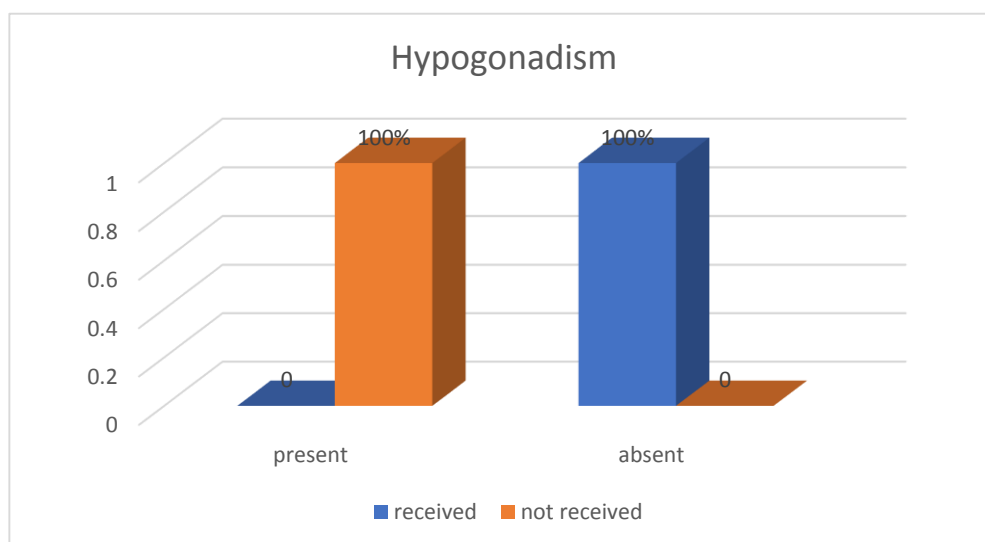
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Table 30 and graph 30 shows association of hypogonadism with chelation therapy. There was a significant association ($p=0.005$) between hypogonadism and chelation therapy.

Table 30: Association of hypogonadism with chelation therapy

Chelation therapy	Hypogonadism (Age>13 years, n=8)		p-value
	Present	Absent	
Received	-	6 (100%)	0.005
Not received	2	-	
Total	2 (100%)	6 (100%)	

Graph 30 : Association of hypogonadism with chelation therapy



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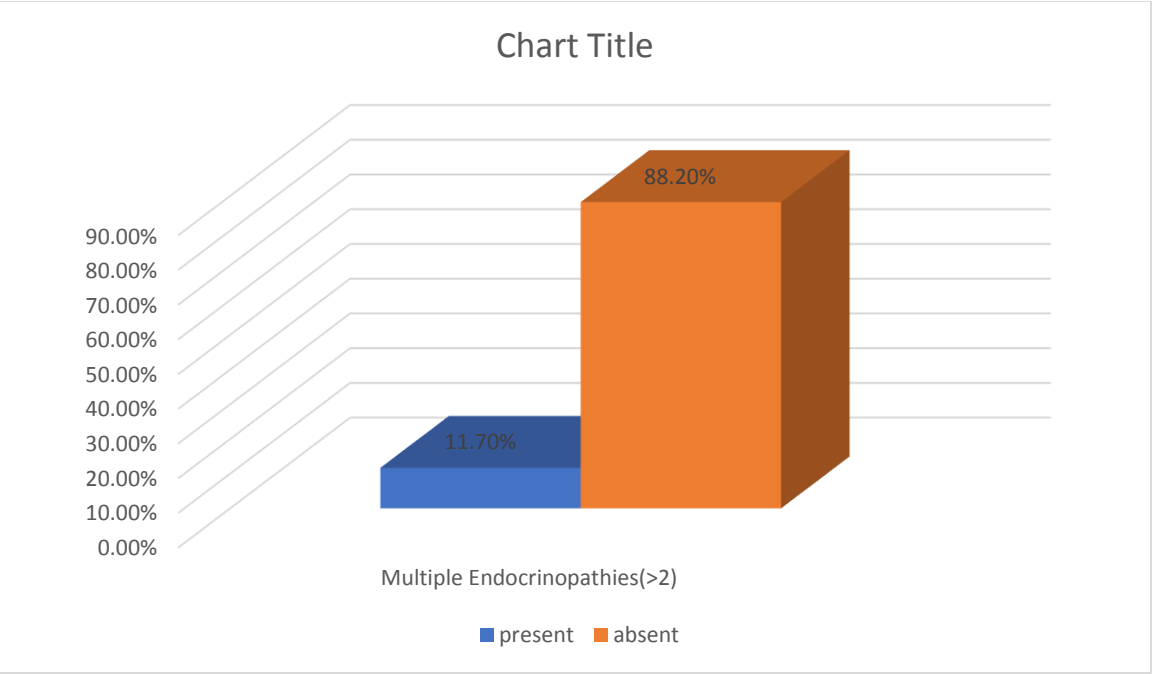
Table 31 and graph 31 shows patients with multiple endocrinopathies (> 2 endocrinopathies).

There were 6 patients with more than 2 endocrinopathies, out of which 2 patients had hypothyroidism, hypocalcemia and hypogonadism, 1 patient had diabetes and hypothyroidism, 2 patients had hypocalcemia and diabetes.

Table 31: Patients with multiple endocrinopathies(n=51):

	Present	Absent
Multiple Endocrinopathies (> 2)	6(11.7%)	45(88.2%)

Graph 31: Patients with multiple endocrinopathies:



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DISCUSSION

Thalassemia major is one of the most common hereditary hemoglobinopathies worldwide, characterized by reduced or absent synthesis of the beta-globin chain leading to ineffective erythropoiesis and chronic hemolytic anemia. The mainstay of treatment involves regular blood transfusions, which though life-saving, results in progressive iron overload in various organs including the endocrine glands. Despite advances in iron chelation therapy, endocrinopathies remain a significant cause of morbidity in children and adolescents with thalassemia major. Endocrine complications generally manifest in the second decade of life but can appear earlier depending on various factors including transfusion burden, adequacy of chelation therapy, and genetic predisposition. The spectrum of endocrine manifestations ranges from growth retardation, delayed puberty, and hypogonadism to diabetes mellitus, hypothyroidism, hypoparathyroidism, and adrenal insufficiency. The present study was undertaken to evaluate the prevalence of various endocrine manifestations in children and adolescents with thalassemia major and to identify the associated risk factors, aiming to formulate appropriate strategies for early detection and intervention.

Demographic and Clinical Characteristics

Age and Gender Distribution

In our study, we observed that the majority of patients (62.7%) were between 5-10 years of age, followed by 21.6% under 5 years and 15.7% between 10-15 years. This age distribution is consistent with the findings of Sharma et al. who reported a similar demographic pattern with 58% of patients between 5-10 years in their cohort of 100 thalassemic children from North India.¹¹³ The gender distribution in our study showed a male predominance (58.8%) which contradicts with the

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observations of Vichinsky E et al. who reported 45% males among 407 transfusion-dependent thalassemia patients.¹¹⁴ This gender disparity could be attributed to social factors in developing countries where male children might receive more medical attention and regular follow-up care.

Transfusion Characteristics

The majority of our patients (74.5%) had initiated blood transfusions before the age of one year, which is slightly higher compared to the findings of Dhouib et al. who reported that 62% of patients in their study from Tunisia had started transfusions before one year of age.¹¹⁵ The frequency of transfusion in our study was predominantly once a month (88.2%), similar to the transfusion protocol followed in many centers across India and other developing countries. Shamshirsaz et al. reported that 91% of their Iranian cohort received transfusions every 3-4 weeks.¹¹⁶ The mean number of transfusions in our patients was 84 ± 38.4 .

Anthropometric Parameters and Clinical Presentation

Growth retardation is a common finding in thalassemia major patients. In our study, 23.5% of patients had weight below the 3rd centile and 29.4% had height below the 3rd centile, while BMI assessment revealed that 37.3% were underweight. These findings are in agreement with Soliman et al. who reported that 32% of thalassemic children in their Egyptian cohort had height below the 3rd centile.¹¹⁷ Growth retardation in thalassemia is multifactorial, attributed to chronic anemia, iron overload affecting growth hormone-insulin-like growth factor axis, nutritional deficiencies, and chelation therapy.

Splenomegaly was observed in 39.2% of our patients, slightly lower than the 48% reported by Thuret et al. in their French cohort.¹¹⁸ This difference could be attributed to the earlier institution of hypertransfusion regimens in developed countries, which delays splenomegaly. Hepatomegaly was present in 37.3% of our patients, consistent with the 46% reported by

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Hashemizadeh H et al.¹¹⁹ The lower prevalence of splenomegaly in our cohort could also be explained by the fact that 5.9% of our patients had undergone splenectomy, similar to the 6.8% reported by Agarwal et al. in their North Indian cohort.¹²⁰

Endocrine Manifestations

Glucose Metabolism Abnormalities

Diabetes mellitus and glucose intolerance are well-recognized complications in thalassemia major. In our study, 25.5% of patients had HbA1c values >6.5%, indicative of diabetes, while 33.3% had values between 5.7-6.4%, suggestive of pre-diabetes. The mean fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) values were 110.4 ± 11.7 mg/dL and 131.8 ± 13.3 mg/dL respectively. These findings are comparable to the study by De Sanctis et al. who reported diabetes in 20.2% and impaired glucose tolerance in 30.6% of their Italian cohort of thalassemia major patients.¹²¹

Interestingly, we found a significant association between HbA1c levels and iron chelation therapy ($p < 0.001$), with all diabetic and pre-diabetic patients receiving chelation, whereas 57.1% of non-diabetic patients had not received chelation. This paradoxical finding might be explained by the fact that patients with higher transfusion burden and consequently greater iron overload require chelation therapy, and these same patients are at higher risk for developing endocrinopathies. Chirico et al. reported similar observations, suggesting that the duration and adequacy of chelation therapy, rather than its mere presence, might be the critical factor in preventing endocrine complications.¹²²

The age of onset of transfusion and frequency of transfusion did not show significant association with HbA1c levels in our study ($p = 0.65$ and $p = 0.06$ respectively). This differs from the findings of Cappellini et al. who observed a significant correlation between the age of first

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transfusion and glucose metabolism abnormalities.¹²³ The discrepancy might be due to differences in sample size, transfusion protocols, and chelation regimens.

Thyroid Dysfunction

Thyroid dysfunction is another common endocrinopathy in thalassemia major. In our study, 9.8% of patients had low T4 levels suggestive of hypothyroidism. TSH was abnormal in 13.7% of patients (9.8% elevated and 3.9% decreased). These findings differ somewhat from those reported by Zervas et al. who found hypothyroidism in 18% of their Greek cohort of thalassemia major patients, with no cases of hyperthyroidism.¹²⁴

We observed no significant association between thyroid dysfunction and chelation therapy ($p=0.19$), where all hypothyroid patients had not received chelation. This suggests a potential role of iron chelators in modulating thyroid function, possibly through altering iron deposition patterns or through direct effects on thyroid hormone synthesis or metabolism. Christoforidis et al. reported improved thyroid function with intensive chelation therapy, supporting the protective role of chelation against thyroid dysfunction.¹²⁵

The age, age of starting transfusion, frequency of transfusion, and serum ferritin levels did not show significant association with thyroid dysfunction in our study. This is in contrast to the findings of Eshragi et al. who reported a significant correlation between serum ferritin levels and thyroid dysfunction in their Iranian cohort.¹²⁶ The discrepancy might be due to variations in sample size, duration of disease, and differences in the definition of thyroid dysfunction.

Hypogonadism

Hypogonadism, characterized by delayed puberty and infertility, is one of the most common endocrinopathies in thalassemia major. In our study, gonadotropin assessment revealed

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low LH in 25% and low FSH in 12.5% of patients (age > 13 years) suggestive of hypogonadotropic hypogonadism. This prevalence is lower than that reported by Multicentre Study on Endocrine Complications in Thalassemia Major (MEECT), which found hypogonadism in 40-50% of thalassemic patients.¹²¹ The lower prevalence in our study might be attributed to the younger age profile of our cohort, as hypogonadism typically manifests during adolescence.

We found a significant association between hypogonadism and chelation therapy ($p=0.005$), suggesting that out of 8 patients (age>13 years), 2 patients had hypogonadism who did not receive chelation therapy. These findings align with those of Borgna-Pignatti et al. who reported increasing prevalence of hypogonadism with age and transfusion burden in their Italian cohort.¹²² The early onset of transfusion dependence indicates a more severe phenotype with greater ineffective erythropoiesis and consequently higher iron overload, predisposing to endocrine complications.

Calcium Homeostasis

Hypocalcemia was observed in 21.6% of our patients, which is comparable to the 22.5% reported by Vogiatzi et al. in their North American cohort.¹²³ Hypocalcemia in thalassemia major is primarily attributed to hypoparathyroidism resulting from iron deposition in the parathyroid glands. Additionally, vitamin D deficiency, which is common in thalassemia patients due to poor nutrition, hepatic dysfunction affecting vitamin D metabolism, and reduced sun exposure, might contribute to hypocalcemia.

Iron Overload and Chelation Therapy

Serum ferritin, a surrogate marker of iron overload, was elevated (>1500 ng/mL) in 90.2% of our patients, similar to the 92% reported by Mishra et al. in their Indian cohort.¹²⁴ High ferritin levels correlate with increased risk of endocrinopathies, though the relationship is not always linear

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due to factors like inflammation, liver disease, and ascorbate deficiency affecting ferritin levels.

Iron chelation therapy was received by 76.5% of our patients, which is lower than the 85% reported by De Sanctis et al. in their international survey.¹²⁵ The lower rate of chelation in our study might be attributed to factors like economic constraints, poor compliance, and limited access to chelation agents in resource-limited settings.

We observed significant associations between chelation therapy and both HbA1c levels and thyroid dysfunction, highlighting the complex relationship between iron chelation and endocrine function. While chelation therapy aims to reduce iron overload and its complications, including endocrinopathies, paradoxically, patients receiving chelation in our study had higher rates of diabetes and hyperthyroidism. This might be explained by the fact that these patients had already accumulated significant iron load before commencing chelation, or that the chelation regimen was suboptimal in terms of timing, dose, or compliance.

Our study also showed 6 (11.7%) patients with more than 2 endocrinopathies, out of which 2 patients had hypothyroidism, hypocalcemia and hypogonadism, 1 patient had diabetes and hypothyroidism, 2 patients had hypocalcemia and diabetes indicating polyendocrine dysfunction in children and adolescents with thalassemia major.

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Clinical Implications and Recommendations

Based on our findings and comparison with existing literature, we propose the following recommendations for the management of endocrine complications in thalassemia major:

1. Regular monitoring of growth parameters and endocrine function should be initiated early, preferably from the age of 5 years, given the significant prevalence of endocrinopathies in the 5-10 years age group in our study.
2. Special attention should be paid to patients who started transfusions before one year of age and those requiring frequent transfusions, as these factors were associated with higher risk of hypogonadism.
3. Intensive and regular iron chelation therapy should be instituted early, before significant iron overload occurs, to prevent endocrine complications. The choice, dose, and combination of chelators should be individualized based on patient's age, iron burden, and organ-specific iron deposition.
4. Regular monitoring of HbA1c, thyroid function tests, and gonadotropin levels should be part of the routine follow-up of thalassemia patients, especially those with high ferritin levels and longer duration of transfusion dependence.
5. Nutritional assessment and supplementation, particularly of calcium and vitamin D, should be an integral part of thalassemia management, given the high prevalence of hypocalcemia in our study.
6. A multidisciplinary approach involving hematologists, endocrinologists, nutritionists, and psychologists is essential for comprehensive management of thalassemia major and its complications.

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Strengths and Limitations

The strength of our study lies in its comprehensive evaluation of multiple endocrine parameters in a relatively large cohort of thalassemia major patients. However, there are several limitations that warrant consideration. First, the cross-sectional design precludes establishment of causal relationships and evaluation of temporal trends in endocrine function. Second, detailed assessment of growth hormone axis, adrenal function, and bone metabolism was not performed, which might have provided a more complete picture of endocrine dysfunction. Third, information on the type, dose, duration, and compliance of chelation therapy was not analyzed in detail, which could have provided insights into the effectiveness of different chelation regimens in preventing endocrinopathies. Fourth, genetic factors, which might influence the susceptibility to endocrine complications, were not assessed.

Conclusion

Endocrine complications are common in children and adolescents with thalassemia major, with glucose metabolism abnormalities, thyroid dysfunction, hypogonadism, and hypocalcemia being the prominent manifestations. Age, age of starting transfusion, frequency of transfusion, and chelation therapy significantly influence the risk of endocrinopathies. Regular monitoring of endocrine function and appropriate intervention are essential for improving quality of life and reducing morbidity in thalassemia major. Future prospective studies with larger sample sizes, longer follow-up, and more detailed assessment of chelation regimens and genetic factors are needed to further elucidate the pathogenesis, prevention, and management of endocrine complications in thalassemia major.

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CONCLUSION

Endocrine complications represent a significant burden in children and adolescents with thalassemia major, affecting their quality of life and long-term prognosis. Our study demonstrates a substantial prevalence of endocrinopathies in the pediatric thalassemic population, with glucose metabolism abnormalities, thyroid dysfunction, hypogonadism, and hypocalcemia being the most prominent manifestations in northern part of Karnataka.

The findings highlight the relationship between transfusion burden, age of onset, and endocrine complications. Patients who started transfusions earlier in life, particularly before one year of age, and those requiring more frequent transfusions were at higher risk for developing endocrine abnormalities. This underscores the importance of careful monitoring of transfusion requirements and their potential impact on endocrine function.

Iron overload, as evidenced by elevated ferritin levels in 90.2% of our patients, emerges as a critical factor in the pathogenesis of endocrinopathies. Despite the institution of chelation therapy in 76.5% of patients, endocrine complications remained prevalent, suggesting that the timing, adequacy, and compliance with chelation regimens are crucial determinants of their efficacy in preventing endocrine dysfunction.

The complex interplay between chelation therapy and endocrine function was evident in our study, with significant associations observed between chelation therapy and both HbA1c levels and thyroid dysfunction. These findings emphasize the need for individualized chelation protocols based on patient characteristics, transfusion burden, and organ-specific iron deposition patterns.

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Growth retardation, reflected in the significant proportion of patients with weight and height below the 3rd centile, remains a concerning issue. The multifactorial nature of growth impairment in thalassemia necessitates a comprehensive approach to its management, encompassing optimal transfusion regimens, effective chelation, nutritional support, and hormonal therapy when indicated.

In conclusion, our study reinforces the critical need for regular monitoring of endocrine function in children and adolescents with thalassemia major, starting from an early age. A multidisciplinary approach involving hematologists, endocrinologists, dietitians, and psychologists is essential for the holistic management of these patients. Early detection and appropriate intervention for endocrine complications can significantly improve growth, development, quality of life, and long-term outcomes in this vulnerable population. Future research should focus on optimizing chelation strategies, exploring novel therapies to prevent and treat endocrinopathies, and elucidating the genetic factors that influence susceptibility to endocrine complications in thalassemia major.

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SUMMARY

INTRODUCTION

Thalassemia major is one of the most common hereditary hemoglobinopathies worldwide, characterized by ineffective erythropoiesis and chronic hemolytic anemia. Regular blood transfusions, though life-saving, result in progressive iron overload affecting various organs including the endocrine glands. Despite advances in iron chelation therapy, endocrinopathies remain a significant cause of morbidity in thalassemia major patients.

AIMS AND OBJECTIVES

Objective:

1. To study the prevalence of endocrine manifestations in patients with thalassemia major and to refer them for required endocrine treatment.

MATERIAL AND METHODS

This prospective cohort study included 51 children and adolescents with thalassemia major attending the thalassemia clinic. Detailed history, anthropometric assessment, clinical examination, and laboratory investigations including complete blood count, serum ferritin, glucose parameters (FBS, PPBS, RBS, HbA1c), thyroid function tests (T3, T4, TSH), serum calcium, and gonadotropin levels (LH, FSH) were performed.

RESULTS

- This study investigated the endocrine manifestations in 51 children and adolescents with thalassemia major. The study population comprised predominantly children aged 5-10

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years (62.7%), with a male predominance (58.8%). The majority of patients (74.5%) had initiated blood transfusions before one year of age, and 88.2% received transfusions once a month, with a mean of 84 ± 38.4 total transfusions.

- Anthropometric assessment revealed growth retardation in a significant proportion of patients, with 23.5% having weight and 29.4% having height below the 3rd centile. BMI evaluation showed that 37.3% of patients were underweight. Clinical examination found pallor in 90.2%, splenomegaly in 39.2%, hepatomegaly in 37.3%, and hemolytic facies in 25.5% of patients. Splenectomy had been performed in 5.9% of cases.
- Evaluation of glucose metabolism showed diabetes (HbA1c $>6.5\%$) in 25.5% and pre-diabetes (HbA1c 5.7-6.4%) in 33.3% of patients. Random blood sugar was elevated in only 5.9% of patients, with mean fasting and post-prandial blood sugar values of 110.4 ± 11.7 mg/dL and 131.8 ± 13.3 mg/dL respectively.
- Thyroid function assessment revealed hypothyroidism (low T4) in 9.8%. TSH was abnormal in 13.7% of patients (9.8% elevated and 3.9% decreased). Gonadotropin assessment showed low LH in 25% and low FSH in 12.5% of patients aged > 13 years, suggestive of hypogonadotropic hypogonadism. Hypocalcemia was present in 21.6% of patients.
- Serum ferritin, a surrogate marker of iron overload, was elevated (>1500 ng/mL) in 90.2% of patients. Iron chelation therapy had been received by 76.5% of the study population.
- Statistical analysis revealed significant associations between HbA1c levels and chelation therapy ($p<0.001$), hypogonadism with chelation therapy ($p=0.005$).

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- These findings highlight the significant burden of endocrine complications in pediatric thalassemia major patients and underscore the importance of regular monitoring and appropriate intervention for these complications.

CONCLUSION:

Endocrine complications are common in pediatric thalassemia major patients, with glucose metabolism abnormalities being the most prevalent. Age, transfusion burden, and chelation therapy significantly influence the risk of endocrinopathies. Regular monitoring of endocrine function and appropriate intervention are essential for improving quality of life and reducing morbidity in these patients.

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ANNEXURE I



BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA
BLDE (DU)/IEC/ 967/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology**, scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "TO STUDY THE ENDOCRINE MANIFESTATIONS IN CHILDREN AND ADOLESCENTS WITH THALASSEMIA MAJOR."

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.MANASI SALUNKHE

NAME OF THE GUIDE: DR. ANILKUMAR SAJJAN, ASSOCIATE PROFESSOR,
DEPT. OF PEDIATRICS.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr. Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail: office@bldedu.ac.in
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ANNEXURE – II

RESEARCH INFORMED CONSENT FORM

BLDEA'S SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &
RESEARCH CENTRE, VIJAYAPURA, KARNATAKA – 586103.

TITLE OF THE PROJECT

**“TO STUDY ENDOCRINE MANIFESTATIONS IN CHILDREN
AND ADOLESCENTS WITH THALASSEMIA MAJOR:
A PROSPECTIVE COHORT STUDY”**

GUIDE: Dr. ANIL KUMAR SAJJAN

ASSOCIATE PROFESSOR

DEPARTMENT OF PEDIATRICS

PG STUDENT: Dr. MANASI SALUNKHE

PURPOSE OF RESEARCH

To study endocrine complications in patients of Thalassemia Major.

PROCEDURE: A detailed clinical history, thorough clinical examination and relevant investigations will be carried out, followed by a final workup of the procedure and planning of the outcome.

***To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
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RISK AND DISCOMFORTS:

I understand that I/my ward may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings, which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will have no direct benefit to me other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to confidentiality. Information of sensitive personal nature will not be part of the medical record but will be stored in the investigations research file. If the data is used for publication in the medical literature or for teaching purposes, no name will be used, and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time; Dr. Manasi Salunkhe at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

***To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
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I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Manasi Salunkhe may terminate my participation in the study after he/she has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of an injury to my child resulting directly from child's participation in this study, the injury will be reported promptly and appropriate treatment would be available to the child. But no further compensation would be provided by the hospital. I understand that by my agreement to participate in this study, I am not waiving off any of my legal rights.

I have explained _____ the purpose of the research, the procedures required and the possible risks of the study to the best of my ability.

Dr. Manasi Salunkhe

Date:

(Investigator)

***To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
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PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that **Dr. Manasi Salunkhe** is doing a study on **“TO STUDY THE ENDOCRINE MANIFESTATIONS IN CHILDREN AND AOLESCENTS WITH THALASSEMIA MAJOR”** at Shri B. M. Patil Medical College Hospital Vijayapura, Karnataka. Dr. Manasi Salunkhe has explained to us the purpose of the research and study procedure. We are willing to allow our child to get treated in Shri B.M. Patil Medical College Hospital, Vijayapura. We have been explained about the study, benefits and possible discomforts in detail in our native language and we understand the same. We are aware that the child will get the best treatment and no compensation like financial benefits will be given, if our child’s condition deteriorates or any untoward event happens, and we will not sue anyone regarding the same. We hereby agree to give our full consent for our child’s participation as a subject in this research projec

(Parents / Guardian)

Date

(Witness to signature)

Date

*To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
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ANNEXURE- III

PROFORMA

- 1) NAME:
- 2) IP NO.
- 3) AGE:
- 4) SEX:
- 5) ADDRESS:
- 6) AGE AT WHICH TRANSFUSION STARTED:
- 7) TOTAL NO. OF TRANSFUSIONS:
- 8) GENERAL PHYSICAL EXAMINATION:
 - WEIGHT:
 - HR:
 - TEMPERATURE:
 - RR:
 - BP:
 - HC:
 - LENGTH/ HEIGHT:
 - BMI:

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9)SYSTEMIC EXAMINATION:

- CVS:
- RESPIRATORY SYSTEM:
- GASTRO – INTESTINAL SYSTEM:
- SPLEENOMEGALY:
- HEPATOMEGALY:
- CNS:

9) INVESTIGATIONS:

- PRE- TRANSFUSION HB:
- T3:
- T4:
- TSH:
- RBS:
- S. FERRITIN:
- S. CALCIUM:
- LH(>13YRS)
- FSH(>13YRS):

10) HAS THE PATIENT RECEIVED IRON CHELATION THERAPY?

- YES
- NO

***To Study the Endocrine Manifestations in Children and Adolescents with Thalassemia Major:
A Prospective Cohort Study***

BIO-DATA OF GUIDE

Name: DR. ANILKUMAR SAJJAN

Date of Birth: 20/07/1984

MBBS: Shri B M Patil Medical College, Vijayapura, R.G.U.H.S. March 2009

MD Paediatrics: J.J.M.Medical College, Davangere, R.G.U.H.S. May-2014

Present Designation: Associate Professor, Dept of Paediatrics, B.L.D. E U's Shri. B.M. Patil Medical College, Vijayapura, Karnataka.

KMC Registration No:82863

Work experience: 10 years

Membership : IAP Bijapur District, National Neonatology Forum , Indian Academy Of Paediatrics.

BIO-DATA OF CANDIDATE

Name: DR. MANASI SALUNKHE

Date of Birth: 13/1/1998

AGE: 27

Qualification: MBBS – R.C.S.M Medical College and Hospital, Kolhapur.

KMC Registration Number:

Presently working as- Post-graduate student/ junior resident at the Department Of Pediatrics,

Address: PG girls hostel

Shri B M Patil Medical College, Hospital & Research Center, Vijayapura, Karnataka

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