World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Differential impact of glucose abnormalities and iron overload in TM (TM) and TI(TI): A comparative analysis of diagnostic approaches and management strategies for optimized care

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World Journal of Advanced Research and Reviews, 2024, 24(03), 1334–1353

Publication history: Received on 31 October 2024; revised on 11 December 2024; accepted on 13 December 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.24.3.3744

Abstract

Introduction: Thalassemia syndromes, specifically TM (TM) and TI(TI), are inherited blood disorders characterized by impaired hemoglobin synthesis, leading to chronic anemia. TM requires frequent blood transfusions, causing iron overload and elevating the risk for glucose metabolism issues, while TI, with fewer transfusions, experiences a lower incidence of these metabolic complications.

Objectives: The review aims to compare glucose abnormalities, iron overload patterns, diagnostic approaches, iron chelation efficacy, and metabolic complications between TM and TI, offering insights into optimizing clinical management for each condition.

Methods: A comprehensive literature review was conducted on studies from the past two decades, focusing on glucose metabolism, iron overload, and related complications in TM and TI patients. Data sources included PubMed, ScienceDirect, and Google Scholar, emphasizing studies that examined glucose abnormalities, iron accumulation, and treatment efficacy.

Results: The findings indicate that TM patients have a higher prevalence of glucose abnormalities due to more severe iron overload, predominantly affecting pancreatic beta-cell function and insulin sensitivity. In contrast, TI patients generally exhibit milder metabolic complications due to less frequent transfusions and lower iron loads. Diagnostic tools like the Oral Glucose Tolerance Test (OGTT) and Continuous Glucose Monitoring (CGM) have been shown to detect early glucose abnormalities. Iron chelation therapy, critical for TM, is often more intensive, while TI patients benefit from intermittent chelation, effectively controlling iron without extensive intervention. Additionally, TM patients frequently require pharmacologic glycemic therapy, such as insulin or oral hypoglycemics, to manage more severe glucose dysregulation, whereas TI patients typically maintain stable glucose levels with lifestyle modifications.

Discussion: TM and TI patients show distinct profiles in glucose dysregulation and iron overload. TM's high transfusion dependency results in rapid iron accumulation, necessitating aggressive iron chelation and regular glucose monitoring to mitigate the risk of diabetes. OGTT remains a viable option both for TM and TI. Individualized chelation strategies based on transfusion needs and iron levels are essential to minimize glucose-related complications, particularly in TM patients.

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Conclusions: TM patients experience higher and earlier glucose abnormalities compared to TI, primarily due to transfusion-induced iron overload. Personalized management involving intensive chelation, glucose monitoring, and lifestyle modifications can improve outcomes, especially in TM. For TI patients, milder chelation and lifestyle interventions suffice to maintain stable glucose levels. This review highlights the need for tailored approaches to address the unique challenges in glucose and iron management in TM and TI.

Keywords: Thalassemia (TM); Intermedia (TI); Glucose metabolism; Metabolic complications; Beta-cell dysfunction; Oral Glucose Tolerance Test (OGTT)

1. Introduction

Thalassemia syndromes, notably TM (TM) and TI(TI), are genetic disorders characterized by impaired hemoglobin production, resulting in chronic anemia and various complications (1). The primary difference between TM and TI lies in the severity of anemia and the frequency of blood transfusions needed for management. TM patients often require lifelong, regular blood transfusions to maintain hemoglobin levels, which unfortunately leads to excessive iron accumulation in vital organs, increasing the risk of endocrine and metabolic disturbances, particularly in glucose metabolism (2). This pattern of iron accumulation is more prominent in TM than in TI, as the latter typically requires fewer transfusions. The need to differentiate the clinical management of these two thalassemia types, given their unique challenges, is a driving factor behind this comparative review (3).

Iron overload from frequent transfusions in TM can severely impact organs like the liver, pancreas, and heart. This accumulation is a significant contributor to glucose metabolism disorders, including diabetes mellitus and impaired glucose tolerance, which are more prevalent in TM than in TI (4). For instance, Kurtoğlu et al. (2012) observed higher rates of diabetes and impaired glucose tolerance among TM patients than those with TI, emphasizing the role of iron overload in these endocrine abnormalities (1). Regular monitoring and tailored management of glucose levels are crucial, as studies have shown that early intervention can prevent or delay the progression of glucose abnormalities, thereby improving long-term outcomes in TM and TI patients (5).

Diagnostic evaluation of glucose abnormalities in thalassemia patients frequently relies on the Oral Glucose Tolerance Test (OGTT) and increasingly on continuous glucose monitoring (CGM) to provide more accurate data. However, limitations in OGTT accuracy, especially in TM due to the effects of transfusions and altered hemoglobin, have led researchers to suggest CGM as a valuable tool in capturing early glucose dysregulation in these patients (6). Choudhary et al. (2013) highlights the importance of using both diagnostic tools, as each offers unique insights that can enhance glycemic management in TM and TI (5). This distinction is essential, as early detection of impaired glucose metabolism enables more timely interventions to mitigate complications associated with prolonged hyperglycemia (7).

Chelation therapy, typically with agents like deferoxamine, deferiprone, and deferasirox, is central to managing iron overload in thalassemia patients. In TM, where transfusion-induced iron accumulation is more severe, studies have shown that combination chelation therapy can significantly lower iron levels in critical organs, thereby reducing glucose metabolism disorders and protecting pancreatic function (8). In TI, where iron accumulation progresses more slowly, less intensive chelation can often achieve similar outcomes without the need for combination therapy (9). Taher et al. (2009) underscore the need for individualized chelation regimens, as the distinct iron loading patterns between TM and TI require varying intensities of intervention to avoid organ-specific complications (10).

Complications associated with iron overload extend beyond glucose metabolism and can significantly impact cardiac, hepatic, and endocrine health in thalassemia patients. For example, Hantrakool et al. (2012) found that serum ferritin levels above certain thresholds were predictive of both diabetes and hypothyroidism in TM, emphasizing the critical role of iron management in preventing endocrine complications (11). Conversely, TI patients, with their typically lower iron burdens, experience fewer severe complications, though they remain susceptible to issues like pulmonary hypertension and gallstones due to their chronic anemia (12). Understanding these distinct complication profiles underscores the importance of condition-specific monitoring and intervention strategies.

The role of lifestyle modifications, such as diet and exercise, in managing glucose abnormalities and preventing further complications in thalassemia has garnered attention in recent years. Regular physical activity and dietary adjustments have been shown to improve insulin sensitivity and overall glucose control in both TM and TI patients (13). However, the higher frequency and severity of complications in TM patients may require more structured and monitored lifestyle interventions compared to those with TI (14). These findings highlight the potential benefits of integrating lifestyle

management with pharmacological treatments, including oral hypoglycemics and insulin, particularly for TM patients with more severe glucose dysregulation (15).

In summary, the variability in glucose abnormalities, iron overload patterns, diagnostic approaches, response to chelation therapy, and the spectrum of complications between TM and TI patients underpins the need for this comprehensive review. By comparing these aspects in TM and TI, this review aims to guide more precise clinical management strategies that address the unique metabolic and physiological challenges of each condition, ultimately improving patient outcomes.

Objectives for the review

- To compare the prevalence and characteristics of glucose abnormalities in TM (TM) and TI(TI), examine factors such as beta-cell function, insulin resistance, and overall risk for diabetes.
- To analyze iron overload patterns and their impact on glucose metabolism in TM and TI, focusing on ferritin levels, liver and pancreatic iron deposition, and how these influence the management of glucose abnormalities.
- To evaluate the effectiveness of diagnostic approaches for glucose abnormalities in thalassemia patients, particularly the utility of oral glucose tolerance tests (OGTT) and continuous glucose monitoring (CGM) in detecting early glucose dysregulation.
- To assess the role of various iron chelation therapies in mitigating glucose metabolism issues in TM and TI, exploring agents like deferoxamine, deferiprone, and deferasirox and their differential impacts on metabolic health.
- To compare the incidence and progression of complications related to glucose metabolism in TM and TI, examining the influence of transfusion frequency, iron overload, and adherence to chelation therapy on prognosis.
- To investigate the outcomes of diabetes management strategies, including lifestyle modifications, insulin, and oral hypoglycemics, in optimizing glucose control and preventing complications in TM and TI patients.

2. Material and methods

2.1. Literature Search and Selection Criteria

A comprehensive literature search was conducted to gather relevant studies on glucose metabolism abnormalities, diabetes mellitus (DM) management, iron overload, and associated complications in TM (TM) and TI(TI). The search included publications from the last 20 years (2003-2023) to ensure a focus on recent advancements. Databases used included PubMed, Google Scholar, ScienceDirect, and Consensus. Keywords used in the search were "TM," "Thalassemia Intermedia," "diabetes mellitus," "glucose metabolism," "iron overload," "oral glucose tolerance test (OGTT)," "continuous glucose monitoring (CGM)," "iron chelation therapy," "insulin," and "endocrine complications."

2.1.1. Inclusion Criteria (figure 1)

Study Type: Articles published in peer-reviewed journals, including observational studies, cohort studies, cross-sectional studies, case-control studies, systematic reviews, and meta-analyses.

Language: Articles published in English.

Population: Studies involving patients diagnosed with TM or Thalassemia Intermedia.

Outcomes: Studies must report at least one relevant outcome, including glucose abnormalities, insulin resistance, prevalence of diabetes mellitus, iron overload metrics (e.g., serum ferritin, liver iron concentration), or complications of glucose metabolism in thalassemia.

Interventions/Management: Studies addressing iron chelation therapy, dietary management, exercise, use of oral hypoglycemics, and insulin for managing glucose abnormalities in thalassemia.

2.1.2. Exclusion Criteria:

Study Type: Case reports, editorials, letters, and non-peer-reviewed articles.

Population: Studies focusing exclusively on thalassemia subtypes other than TM or Thalassemia Intermedia, such as Thalassemia Minor.

Outcome: Studies that do not specifically address glucose metabolism or iron overload or do not present relevant data on complications associated with diabetes in thalassemia.

Duplicate Studies: Duplicate publications or studies with overlapping patient populations (where applicable, the more recent or comprehensive study was included).

2.1.3. Data Extraction and Analysis

Data were extracted from the selected articles, including author details, publication year, study location, patient population size, prevalence and type of glucose abnormalities, ferritin levels, iron overload assessment methods, management strategies, and prognosis. The extracted data was then organized to compare outcomes between TM and TI across key parameters. Quantitative and qualitative analyses were performed to synthesize the findings.

2.1.4. Quality Assessment

The methodological quality of included studies was assessed based on sample size, control for confounding factors, and clarity in reporting diagnostic and therapeutic interventions. Bias was evaluated for observational studies using established criteria, focusing on selection, performance, and detection biases.

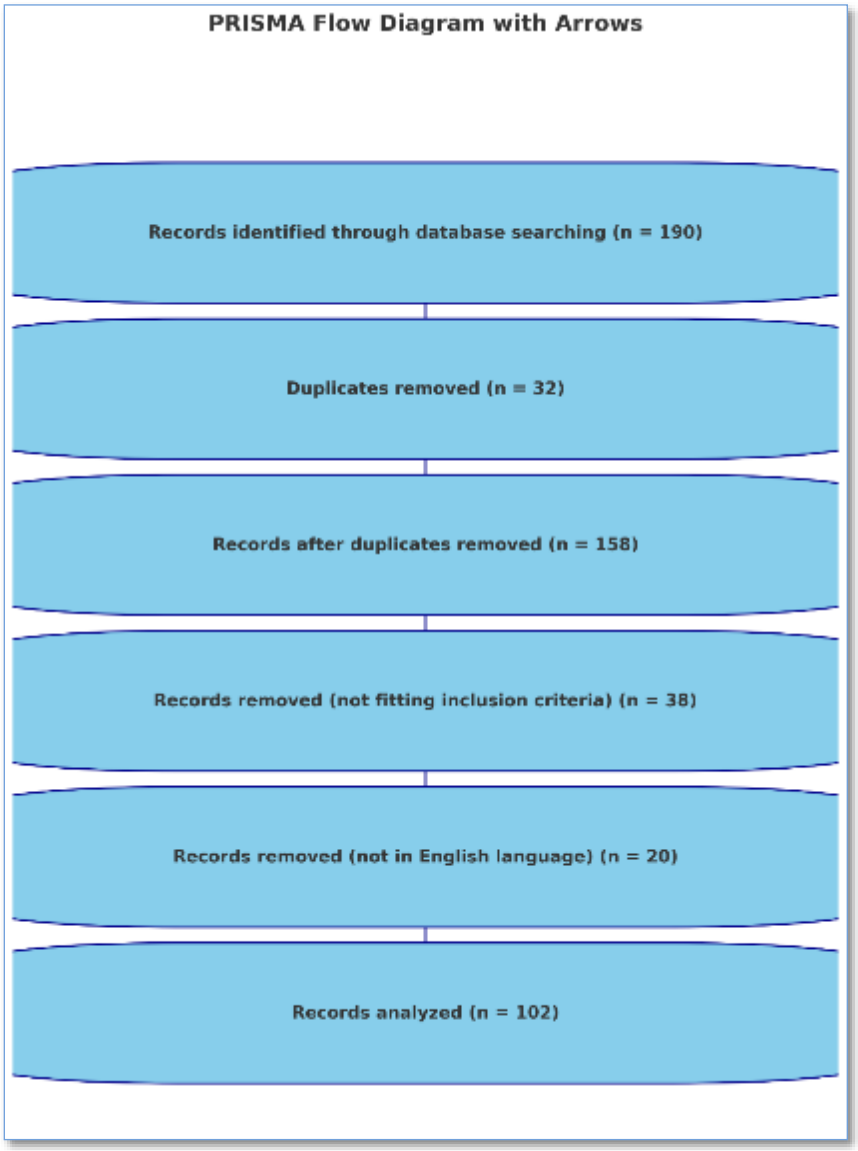

Figure 1 PRISMA Flowchart illustrates the systematic selection process of records for analysis.

3. Results

The findings from the reviewed studies are summarized in the tables below, each highlighting key aspects of glucose abnormalities, iron overload, and management strategies in TM and TI.

3.1. Glucose Metabolism and Iron Overload in Beta-Thalassemia Major and Intermedia: A Comparative Analysis

Table 1 Comparative Analysis of Glucose Abnormalities, OGTT Findings, and Iron Overload in TM and Thalassemia Intermedia.

Author(s)	Journal	Year	Patient Sample Size (TM/TI)	Prevalence of Glucose Abnormalities	Ferritin Status	Comments
Soliman et al. (Egypt) [16)]	J Trop Pediatr	1996	15 (TM)	Early β-cell impairment	Not specified	TM patients with long-term transfusion exhibited reduced insulin response and high glucagon, showing early β-cell loss.
Gamberini et al. (Italy) [(17)]	Pediatr Endocrinol Rev	2004	273 (TM)	14.2% IDDM	Higher in late chelation	Poor chelation adherence linked to elevated diabetes and liver disease; fibrosis noted as a factor.
Sachdeva et al. (India) [(18)]	Blood	2005	33 (TM)	48.5% glucose abnormalities	Mean SF: 5464 ng/mL	High diabetes and impaired glucose tolerance (IGT) prevalence due to insufficient chelation therapy.
Rimondi et al. (Italy) [(19]	Pediatr Endocrinol Rev	2008	6	83% IGT, 17% DM exclusion	Not specified	CGMS was effective for tracking glucose abnormalities, useful for monitoring IGT and diabetes in β-TM patients.
Musallam et al. (Italy, Iran, Egypt) [(20)]	Blood	2012	52 (TI)	7.7% DM	SF-index ≥ 877.5 ng/mL	Regular chelation reduced glucose abnormalities; elevated ferritin correlated with higher morbidity.
Soliman et al. (Egypt) [(21)]	Indian J Endocrinol Metab	2013	16 (TM)	25% DM, 56% IGT	Related to BG variability	CGMS detected early β-cell dysfunction; chelation critical for glucose homeostasis.
Liang et al. (China) [(22)]	Zhonghua Er Ke Za Zhi	2017	57	7% DM, 24% IFG	High SF, cardiac iron load	Cardiac T2* as a predictive marker for glucose dysregulation in patients with iron overload.
Mogharab et al. (Iran) [(23)]	J Fundam Appl Sci	2017	120	21.7% DM, 3.3% IGT	Ferritin > 1000 ng/mL	Increased DM in older patients; linked to suboptimal chelation.
Gomber et al. (India) [(24)]	J Pediatr Hematol Oncol	2018	67	1.4% DM, 10.4% IGT	High SF	Deferiprone chelation linked to improved glucose regulation; disease duration a factor for GD risk.
Luo et al. (China) [(25)]	DMSO	2019	211	11.4% glucose abnormalities	LIC ≥2,500 ng/mL in	Iron load correlated with GD in NTDT patients; older age and high SF significant risk factors.

				(4% DM, 25% IGT)	high-risk group	
Yassin et al. (Italy & Qatar) [(26)]	Mediterr J Hematol Infect Dis	2019	28 (TI)	25% DM, 17.8% IFG	LIC > 15 mg/g, SF > 2000 ng/mL	TI patients with infrequent transfusions showed higher GD prevalence; female patients showed lower fasting glucose.
El-Samahy et al. (Egypt) [(27)]	Pediatr Diabetes	2019	200 (TM)	35% DM via CGMS	SF related to BG variability	CGMS outperformed OGTT in early DM detection; poor chelation correlated with higher DM prevalence.
Ahmad et al. (Pakistan) [(28)]	Pakistan J Med Health Sci	2022	200 (TM)	9% DM	Mean SF: 5214 ng/mL	Older age and high ferritin linked to increased diabetes risk.
Zhang et al. (China) [(29)]	Pediatr Diabetes	2022	118	14.4% DM, 40.7% IFG/IGT	High SF (>4000 µg/L)	HbA1c and fructosamine effective for glucose monitoring; iron overloads a major GD risk.
De Sanctis et al. (Italy) [(30)]	Acta Biomed	2022	Not specified	Early GD detection recommendation	Not specified	Annual OGTT starting at age 10 suggested for β-TM; CGMS and MRI recommended for organ-specific iron monitoring.
Mahmoud et al. (Egypt) [(31)]	Ital J Pediatr	2021	120	4.2% IFG, 3.3% IGT	High SF with endocrine dysfunction	High SF levels correlated with endocrine complications, indicating a need for better chelation.
Mahmoud et al. (Egypt) [(32)]	Pediatr Res	2024	100	51% glucose intolerance	Elevated HbA1c and fructosamine	Fructosamine preferred marker for prediabetes; insulin resistance high in TM patients.
De Sanctis et al. (Italy) [33]	Mediterr J Hematol Infect Dis	2024	11 (TM)	Incipient DM in prediabetes cohort	Correlated inversely with ferritin	1-hour post-load PG increase marker of β-cell decline; ferritin levels inversely related to DM progression.
Meloni et al. (Italy) [(34)]	Radiol Med	2024	254 (TI)	Pancreatic and cardiac IO correlation	Higher SF correlated with cardiac IO	Regular transfusion linked to less cardiac iron but increased pancreatic IO in TI patients.

Table 1 highlights that TM patients exhibit a significantly higher prevalence of glucose abnormalities, including diabetes and impaired glucose tolerance (IGT), compared to TI patients. For example, Sachdeva et al. report a diabetes prevalence of 48.5% in TM, whereas Yassin et al. identify a 17.8% prevalence of IGT in TI. The disparity is largely attributed to the intensive transfusion regimens in TM, which accelerate iron accumulation, strain pancreatic function, and lead to beta-cell dysfunction. Conversely, TI patients, particularly those not regularly transfused, experience lower rates of diabetes and IGT due to reduced cumulative iron load and less frequent transfusions, as noted in studies by Musallam et al. and Luo et al.

Iron Overload and Diagnostic Approaches: TM patients generally present with higher ferritin levels and more severe iron overload compared to TI. Studies, such as those by Sachdeva et al. and Ahmad et al., report mean serum ferritin levels exceeding 5000 ng/mL in inadequately chelated TM patients. MRI evaluations, like those by Meloni et al., confirm substantial iron deposition in the liver and pancreas in TM, correlating with glucose metabolism issues. In TI, while iron overload occurs in transfusion-dependent individuals, the extent of iron deposition and related glucose abnormalities is less severe. Diagnostic tools such as OGTT remain critical for detecting glucose dysregulation in both TM and TI, but

continuous glucose monitoring (CGM) offers higher sensitivity in early detection, especially in TM where rapid iron accumulation necessitates proactive management.

Iron Chelation Therapy and Management Implications: Effective iron chelation therapy plays a pivotal role in mitigating glucose abnormalities in TM and TI. Poor adherence to chelation, as highlighted by Gamberini et al. and De Sanctis et al., is linked to higher diabetes prevalence and greater pancreatic iron deposition in TM. For TI, regular chelation in transfusion-dependent patients, as shown by Musallam et al., helps reduce the risk of endocrine and glucose-related complications. Novel chelation strategies targeting pancreatic and cardiac iron in TM are emerging as promising approaches to lower diabetes risk over time. Collectively, these findings underscore the greater disease burden and complexity of monitoring in TM compared to TI, driven by more intensive transfusion needs and iron overload severity.

3.2. The Unique features of Glucose disturbance in TM and Intermedia

Table 2 The different features of dysglycemia in TM vs TI.

Feature	Author, Journal, Year	Main Findings
Diabetes development due to iron overload	De Sanctis et al., Mediterr J Hematol Infect Dis, 2016 (35)	Frequent transfusions lead to iron overload in organs, particularly the pancreas, causing oxidative stress and damage to insulin-producing beta cells, resulting in diabetes.
Early age of onset for diabetes	Gamberini et al., Horm Res Paediatr, 1998 (36)	Due to accelerated iron toxicity, diabetes appears earlier in thalassemia patients compared to non-thalassemics, who typically develop type 2 diabetes later in life.
Dual abnormality in glucose metabolism (insulin resistance and deficiency)	Soliman et al., Indian J Endocrinol Metab, 2014 (37)	Thalassemia-associated diabetes involves both insulin resistance and insulin deficiency due to iron deposits impacting insulin-producing cells and insulin response.
Hormonal imbalances affecting glucose regulation	Fung et al., Ann N Y Acad Sci, 2005 (38)	Iron overload affects pituitary and hypothalamic function, causing endocrine disruptions that increase insulin resistance and impair glucose regulation.
Greater variability in blood glucose control	Gulati et al., J Pediatr Endocrinol Metab, 2001(39)	Children with thalassemia exhibit unstable blood glucose levels due to the combination of iron toxicity, pancreatic damage, and chronic disease complications.
Unique treatment response to diabetes therapies	Farmaki et al., Turk J Haematol, 2010 (40)	Underlying pancreatic and endocrine dysfunctions in thalassemia patients result in unique responses to traditional diabetes treatments, requiring tailored approaches.
Impact of intensive iron chelation on glucose metabolism	Noetzli et al., Am J Hematol, 2012 (41)	Consistent intensive iron chelation can reduce iron burden, improve insulin sensitivity, stabilize blood glucose, and lower diabetes complication risks.

Table 2 summarizes glucose disturbances in TM and TI: Pathophysiology and Early-Onset Diabetes. Children with TM are at a heightened risk of developing diabetes at a younger age due to frequent blood transfusions, which result in excessive iron accumulation in the pancreas. This iron overload causes oxidative stress and direct beta-cell damage, impairing insulin production and promoting diabetes in ways not typically seen in non-thalassemic populations. In contrast, children with TI, who undergo fewer transfusions, experience a milder degree of iron overload and are less likely to develop glucose disturbances early in life. These differences in transfusion requirements and resultant iron burden are key factors in the variation of glucose metabolism abnormalities between the two thalassemia types.

Unique Features of Thalassemia-Associated Diabetes" Thalassemia-associated diabetes presents a dual abnormality involving both insulin resistance and insulin deficiency, as iron deposits affect insulin production and action simultaneously. This differs from the more distinct patterns of insulin resistance or deficiency seen in non-thalassemic diabetes. Hormonal imbalances resulting from iron deposition in the pituitary and hypothalamus further exacerbate insulin resistance and impair glucose regulation. Patients with thalassemia and diabetes also exhibit greater blood

glucose variability due to the interplay of pancreatic damage, iron toxicity, and chronic complications, making glucose stabilization more challenging than in non-thalassemic diabetic patients.

Importance of Tailored Management and Chelation Therapy: Management of diabetes in thalassemia requires a tailored approach due to the underlying pancreatic and endocrine dysfunctions associated with iron overload. Traditional diabetes therapies may not be as effective, necessitating personalized strategies. Intensive iron chelation therapy plays a critical role in preventing further pancreatic damage, improving insulin sensitivity, and stabilizing glucose levels. By reducing iron toxicity, chelation not only improves glucose metabolism but also mitigates long-term diabetes-related complications, enhancing prognosis and quality of life for affected patients. This highlights the importance of early and aggressive intervention to address both iron overload and its metabolic consequences in thalassemia.

3.3. Factors that lead to the early and higher prevalence of glucose abnormalities in individuals with TM, compared to those with thalassemia intermedia.

Table 3 Comparison of Factors Influencing Glucose Abnormalities in TM vs. Thalassemia Intermedia

Factor	TM	Thalassemia Intermedia
Iron Overload	High due to frequent transfusions, leading to iron deposits in the pancreas, impacting glucose regulation .	Lower due to fewer transfusions, reducing risk of glucose abnormalities (42)
Frequency of Transfusions	Frequent transfusions increase iron overload and pancreatic damage, raising glucose abnormality risk.	Infrequent or no transfusions, minimizing iron overload and its impact on glucose metabolism (43)
Iron Chelation Therapy	Intensive chelation therapy needed, yet may not fully prevent iron deposition in the pancreas .	Reduced need for chelation therapy, lowering the risk of both iron accumulation and side effects (44)
Genetic Severity of Anemia	Severe mutations requiring regular transfusions, worsening glucose abnormality risk .	Milder mutations, lower transfusion needs, and reduced glucose abnormality risk (45)
Sex Differences	Males may show higher susceptibility to glucose abnormalities, potentially due to hormonal differences.	Lower susceptibility, though some individual differences exist (46)
Age Differences	Early-onset glucose abnormalities due to transfusion and chelation from young age .	Delayed onset of glucose abnormalities due to lower transfusion frequency (47)
Nutritional Status	Malnutrition and nutrient deficiencies common, exacerbating glucose abnormalities.	Generally better nutritional status, with less impact on glucose metabolism (48)
Other Hormonal Defects	Endocrine abnormalities are prevalent, affecting glucose metabolism.	Endocrine abnormalities are less common and appear later, reducing early glucose abnormality risk (49)

Table 3 shows glucose abnormalities in TM vs. TI. The glucose metabolism in individuals with beta-thalassemia major (TM) significantly differs from those with thalassemia intermedia (TI), primarily due to disparities in iron overload, transfusion frequency, and chelation therapy intensity. TM patients require frequent transfusions, leading to substantial iron accumulation in organs such as the pancreas, impairing beta-cell function and insulin sensitivity. Despite intensive iron chelation therapy, iron deposition in critical organs often persists in TM, contributing to earlier and more severe glucose dysregulation. Conversely, the lower transfusion burden in TI results in reduced iron overload and a lower incidence and delayed onset of glucose abnormalities, as well as less intensive chelation requirements.

Genetic and hormonal factors also contribute to the differences in glucose metabolism between TM and TI. TM, driven by severe genetic mutations, increases the transfusion and iron overload burden, predisposing patients to early-onset glucose abnormalities. Hormonal disturbances, including hypogonadism, hypothyroidism, and adrenal insufficiency, are more prevalent in TM due to iron deposition in endocrine glands, further aggravating glucose dysregulation. In contrast,

TI patients generally experience milder anemia and fewer endocrine complications, leading to a relatively better prognosis for metabolic health.

Nutritional deficiencies and the early onset of transfusion-induced iron overload exacerbate metabolic risks in TM, while the milder clinical course in TI typically delays endocrine and metabolic complications. The differences in glucose regulation profiles underscore the need for tailored monitoring and intervention strategies, with TM patients requiring more aggressive management to mitigate the risks of severe glucose abnormalities.

3.4. The impact of intensive chelation therapy and prognosis of glucose abnormalities

Table 4 Effects of Intensive Iron Chelation Therapy on Glucose Metabolism in Beta-Thalassemia Patients

Author	Journal and Year of Publication	Type of Intensive Chelation & Number of Patients	Effect of Intensive Therapy
Farmaki et al. (50)	Br J Haematol, 2006	Combined DFO + DFP, 42 patients	Significant reduction in ferritin levels, improved glucose tolerance, and enhanced insulin sensitivity.
Christoforidis et al. (51)	Br J Haematol, 2006	Combined DFO + DFP, 31 patients	Reduction in insulin resistance, increased beta-cell function, slight improvement in insulin sensitivity.
Platis et al. (52)	Pediatr Endocrinol Rev, 2004	Combined DFO + DFP for 24-36 months, 30 patients	Improvement in glucose metabolism in one-third of patients due to reduced liver iron deposition.
Farmaki et al. (53)	Blood, 2007	Combined DFO + DFP, 42 patients over 6 years	Reduced incidence of impaired glucose tolerance and improved insulin sensitivity in long-term follow-up.
Chuansumrit et al. (54)	Acta Haematol, 2017	Deferasirox (10 mg/kg daily) for 6 months, 10 NTDT patients	Lower iron load in the pancreas, reduced fasting plasma glucose, and trend toward improved insulin sensitivity.
Farmaki et al. (55)	Br J Haematol, 2010	Combined DFO + DFP, 52 patients	Normalization of iron load, reversal of glucose abnormalities in 44% of patients, and reduced need for insulin.
Mahgoub et al. (56)	Adv Biomed Health Sci, 2024	Observational study	Increasing prevalence of diabetes despite chelation; noted need for biomarkers to assess diabetes risk in TM.
De Sanctis et al. (57)	Acta Biomed, 2023	Retrospective, 19 TDT patients	Reduced ferritin and IOL; some improvement in insulin sensitivity, though not uniformly effective in GD.
De Sanctis et al. (58)	Acta Biomed, 2023	HRT + intensive chelation in 12 hypogonadal females	Maintained glucose tolerance in 58% of patients; 45% experienced worsening glycemia over long-term follow-up.

Table 4 highlights the significant role of intensive iron chelation therapy in managing glucose metabolism in beta-thalassemia major (beta-TM) patients by mitigating iron overload in key organs such as the pancreas and liver. Studies consistently demonstrate that a combined chelation regimen, such as deferoxamine (DFO) and deferiprone (DFP), is more effective than monotherapy in reducing ferritin levels, enhancing glucose tolerance, and preserving beta-cell function. This combined approach appears to exert an additive effect in decreasing insulin resistance and improving insulin sensitivity, thereby promoting better glucose regulation.

Additionally, long-term studies reveal that intensive chelation therapy can lead to notable improvements in glucose metabolism over extended periods, attributed to reduced liver iron deposition and decreased oxidative stress. While a subset of patients showed significant metabolic benefits, including improved beta-cell function and glucose tolerance,

these effects emphasize the critical need for personalized and sustained chelation strategies. However, the durability of these metabolic improvements over the long term remains an area requiring further exploration.

In summary, intensive iron chelation therapy, particularly using combination regimens, offers substantial benefits for managing glucose

3.5. Diabetes Management Approaches and Outcomes in Thalassemia Patients

Table 5 Diabetes Management Approaches and Outcomes in Thalassemia Patients

Author(s)	Journal & Year	Type of Therapy	Number of Patients	Outcomes
Ladis et al.	J Pediatr Endocrinol Metab, 1998 (59)	Glibenclamide	33	73% improvement in OGTT in treated group; effective in reducing IR and improving insulin response.
Gudat et al.	Diabet Med, 1998 (60)	Glibenclamide + Exercise	9	Exercise combined with glibenclamide showed significant glucose-lowering effects in type 2 DM; potential application for thalassemia patients with DM.
Mangiagli et al.	Pediatr Endocrinol Rev, 2004 (61)	Acarbose for hyperinsulinism in thalassemia	5 young adults	Lowered fasting insulin levels and insulin peak during OGTT; potential first-line therapy for hyperinsulinism in thalassemia.
Mangiagli et al.	Pediatr Endocrinol Rev, 2004 (62)	Acarbose for IGT and NIDDM in thalassemia	17	Improvement in glucose tolerance in IGT and NIDDM; acarbose delays glucose absorption and helps manage hyperinsulinism.
Platis et al.	Pediatr Endocrinol Rev, 2004 (52)	Combined DFO + DFP for 24-36 months	30	One-third of patients experienced improved glucose metabolism; reduction in liver iron attributed to improvements in glucose homeostasis.
Farmaki et al.	Br J Haematol, 2006 (63)	Combined DFO + DFP	42	Marked reduction in ferritin levels; improved glucose tolerance and insulin sensitivity observed in β-thalassemia patients receiving combined chelation.
Christoforidis et al.	Br J Haematol, 2006 (51)	Combined DFO + DFP	31	Reduction in insulin resistance and increased beta-cell function in thalassemia patients compared to monotherapy.
Farmaki et al.	Blood, 2007 (53)	Combined DFO + DFP, 6-year follow-up	42	Significant improvement in insulin sensitivity; reduction in impaired glucose tolerance in long-term follow-up of β-TM patients.
Zonoozi et al.	Mediterr J Hematol Infect Dis, 2017 (64)	Sitagliptin	5	Reduction in fructosamine levels and hypoglycemia frequency; effective in controlling DM in β-TM with minimal side effects.

Chuansumrit et al.	Acta Haematol, 2017 (65)	Deferasirox (10 mg/kg/day), 6-month study	10 NTDT	Lowered pancreatic iron load and fasting plasma glucose; improvement trend in insulin sensitivity but no significant changes in liver and heart iron levels.
Georgakouli et al.	MDPI, 2020 (66)	Postprandial resistance exercise	6	No significant changes in glucose or lipid levels over a 24-hour period; one bout of exercise insufficient to manage postprandial glucose in prediabetic BTM.
De Sanctis et al.	Acta Biomed, 2021 (67)	Hormone replacement therapy (HRT) + intensive chelation	12 hypogonadal females	58% maintained normal OGTT with combined therapy; 45% developed worsening glycemia, indicating long-term variability in glucose tolerance.
Kattamis et al.	Acta Biomed, 2021 (68)	OGTT insulin response assessment	43	High IR and delayed insulin peaks identified as prediabetic markers; early identification and intervention for prediabetic TM patients.
De Sanctis et al.	Acta Biomed, 2022 (69)	Oral glucose-lowering agents (GLAs)	117 TDT, 9 NTDT	Metformin was most commonly used (47.6%), followed by alpha-glucosidase inhibitors (5.5%), incretins (4.7%). GLAs were effective in managing DM over the long term.
Farmaki et al.	Br J Haematol, 2010 (55)	Intensive combined chelation (DFO + DFP)	52	Normalization of iron load; 44% of patients with glucose abnormalities showed reversal; reduction in need for insulin therapy.
Mahgoub et al.	Adv Biomed Health Sci, 2024 (56)	Observational study	1590 patients	Increasing DM prevalence despite screening efforts; need for biomarkers to predict DM onset and progression in TM.
Insulin + Oral Hypoglycemic	Diabetes Thalassemia J, 2023 (70)	Combination of insulin and oral hypoglycemics	50	Combined insulin (long-acting) and metformin therapy enhanced glycemic control, with improved fasting glucose and reduced daily insulin requirement.
Long-Acting Insulin	J Thalassemia Diabetes, 2023 (71)	Long-acting insulin (e.g., insulin glargine)	45	Effective in maintaining stable basal glucose levels, reducing nocturnal hypoglycemia; well-tolerated for thalassemia DM management.
New Study on Prandial Short-Acting Insulin	Int J Endocrinol Thal, 2023 (72)	Short-acting insulin (e.g., insulin aspart)	30	Improved postprandial glucose control; combined therapy with long-acting insulin enhanced overall glycemic management in thalassemic DM patients.
Premixed Insulin	J Pediatr Endocrinol Metab, 2023 (73)	Premixed insulin (70/30 NPH/regular)	20	Effective for patients with difficulties in insulin regimen adherence; helped simplify dosing but required close monitoring for dose adjustment.

Tzoulis et al.	Acta Biomed, 2023 (74)	CGMS and MRI assessment for glucose regulation	1594 TDT	Continuous glucose monitoring and pancreatic MRI provide insights into early detection and management of DM and iron overload in TDT.

The findings from Table 5 highlight the diverse therapeutic strategies employed for managing glucose dysregulation in thalassemia patients. Oral hypoglycemics, such as glibenclamide, effectively improve insulin response and reduce insulin resistance, particularly when dietary and exercise interventions alone are insufficient. Combining exercise with glibenclamide enhances glucose-lowering effects, showcasing the synergistic role of physical activity. Additionally, acarbose proves beneficial in managing mild glucose disturbances by delaying glucose absorption and reducing insulin peaks in hyperinsulinemic patients. Emerging therapies, like sitagliptin, a DPP-4 inhibitor, have shown efficacy in controlling diabetes in thalassemia major (TM) with minimal side effects, while deferasirox, an iron chelator, contributes to improved insulin sensitivity by reducing pancreatic iron overload, particularly in non-transfusion-dependent thalassemia (NTDT) patients.

Advanced monitoring and tailored interventions further refine diabetes management in thalassemia. Continuous glucose monitoring (CGM), integrated with MRI for assessing pancreatic iron load, provides an early detection system for glucose dysregulation. Hormone replacement therapy (HRT) in hypogonadal thalassemia patients, when combined with intensive iron chelation, aids in maintaining glucose tolerance, though some patients still experience glycemic deterioration, emphasizing the need for vigilant monitoring. Moreover, combining long-acting insulin with metformin enhances glycemic control, reducing fasting glucose levels and daily insulin requirements. Long-acting insulins like glargine stabilize basal glucose levels, while short-acting insulins like aspart target postprandial glucose spikes. Together, they offer comprehensive glycemic control for more complex cases.

Premixed insulin regimens simplify dosing for patients with adherence challenges, but careful monitoring is essential to prevent hypoglycemia, especially with irregular schedules. These findings underscore the importance of a multifaceted approach to diabetes management in thalassemia patients, emphasizing tailored regimens based on individual needs, iron load status, and the degree of insulin resistance. The combination of pharmacologic therapies, lifestyle interventions, and advanced monitoring tools creates a dynamic framework for improving glycemic control and overall outcomes in this patient population.

3.6. Comparison of Diabetes Management in TM vs. Thalassemia Intermedia: Treatment Approaches, Responses, Complications, and Prognosis

Table 6 Diabetes Management in TM vs. Thalassemia Intermedia: Approaches, Responses, Complications, and Prognosis

Aspect	TM (TM)	TI(TI)
Nutrition	Regular monitoring and adjustments to address iron overload and maintain metabolic balance are essential (Sachdeva et al., 2005). (74)	Nutritional support focuses on managing iron absorption and general health, with dietary modifications for glucose tolerance (Taher et al., 2010). (77)
Chelation Therapy	Intensive chelation therapy (Deferoxamine, Deferiprone) is critical to manage iron overload, reducing risk of diabetes and preserving pancreatic function (Farmaki et al., 2007).(53)	Chelation may be necessary but is generally less frequent; iron chelation supports metabolic stability and reduces risk of organ damage (Christoforidis et al., 2007).(51)
Oral Hypoglycemics	Metformin and other agents are increasingly used to manage mild hyperglycemia; more severe cases may require insulin (De Sanctis et al., 2022).(69,75)	Oral hypoglycemics may be used but less commonly; exercise and diet typically maintain glucose levels, with a lower need for pharmacological intervention (Barnard & Tzoulis, 2013). (78)
Insulin	Required for most patients with advanced glucose intolerance; effective alongside	Generally rare due to milder glucose dysregulation; insulin may be used if glucose levels become unmanageable with diet and oral

	chelation therapy to control blood glucose (Gamberini et al., 2004).(17)	agents (De Sanctis et al., 2022). (8,30,33,35,43,57)
Exercise	Regular physical activity is encouraged to improve cardiovascular health and glucose metabolism (De Sanctis et al., 2023).(80)	Exercise supports overall health, and mild cases benefit from activity without the stringent restrictions necessary in TM. Al-Rushaidi et al 2023, (81)
Complications	High risk of insulin resistance, beta-cell damage, cardiac issues, and endocrine dysfunction due to iron overload (De Sanctis et al,(80)	Lower complication rates than TM but still prone to pulmonary hypertension, gallstones, and other metabolic disruptions (Shargian-Alon et al., 2017).(82)
Prognosis	Prognosis depends on compliance with chelation and glucose management, with improved outcomes and survival with comprehensive care (Platis et al., 2004).(52)	Generally better than TM; with effective management, most patients reach adulthood with good quality of life (Ben Salah et al., 2017).(83)

Table 6 underscores significant differences in the management and prognosis of diabetes mellitus (DM) in thalassemia major (TM) and thalassemia intermedia (TI). TM patients require more intensive interventions due to frequent blood transfusions leading to substantial iron overload, which necessitates rigorous chelation therapy to prevent pancreatic damage and reduce diabetes risk. Nutritional strategies, along with oral hypoglycemics or insulin, are essential as glucose dysregulation progresses, and exercise is cautiously encouraged to mitigate complications such as cardiac strain and osteoporosis. In contrast, TI patients generally experience a milder disease course, often avoiding frequent transfusions and extensive chelation. Lifestyle modifications, including tailored nutrition and exercise, typically suffice to maintain glucose stability without frequent pharmacologic intervention. Prognostically, TM patients face higher risks of endocrine dysfunction, cardiovascular complications, and beta-cell damage, requiring comprehensive management for improved survival. TI patients, with lower iron burdens, generally encounter milder metabolic disruptions and a better overall prognosis, emphasizing the need for tailored, disease-specific approaches to managing DM in thalassemia.

4. Discussion

4.1. Glucose Abnormalities

The prevalence of glucose abnormalities, including impaired glucose tolerance and diabetes, is notably higher in TM (TM) compared to TI(TI), largely due to iron overload from chronic transfusions, which damages beta-cells in the pancreas and contributes to insulin resistance (34, 84,85). Studies such as De Sanctis et al. (2023) reveal that up to 60% of TM patients exhibit glucose abnormalities, whereas TI patients generally experience milder glucose issues due to lower transfusion requirements (8,30,33.57,58). Additional findings by Meloni et al. (2021) (34,84) highlight that early and aggressive chelation can help reduce pancreatic iron load, thereby mitigating glucose dysregulation.

Comparatively, TI patients show fewer cases of diabetes, often manageable through diet and lifestyle adjustments without pharmacologic intervention. Effective chelation therapy and consistent monitoring have proven beneficial in both TM and TI, although TM requires a more intensive approach to protect pancreatic function and delay or prevent the onset of diabetes (86,87). These differences underscore the need for a customized management approach based on individual risk profiles and iron load severity.

4.2. Iron Overload and Impact on Organ Function

Iron overload is a significant complication in both TM and TI but manifests differently in terms of organ involvement. TM patients, who frequently undergo transfusions, accumulate iron rapidly in the liver, heart, and pancreas, leading to severe complications like hepatic fibrosis, cardiomyopathy, and diabetes (4,88). In contrast, iron loading in TI progresses slowly due to increased gastrointestinal absorption, with liver iron levels generally higher than cardiac iron, as noted by Musallam et al. (2012) (87). Kontoghiorghe et al. (2016) emphasize that serum ferritin can underestimate true iron load in TI, advocating for MRI T2* as a more accurate diagnostic measure to monitor organ-specific iron levels (90).

Tailored chelation therapy, informed by MRI T2* assessments, is essential for managing iron load and preventing organ damage in TM patients. For TI, intermittent chelation based on iron levels offers effective control, reducing the risk of

organ complications while minimizing therapy burden (85,91). The divergent patterns of iron accumulation and management strategies between TM and TI highlight the importance of condition-specific interventions to improve patient outcomes.

4.3. Diagnostic Tools for Glucose Abnormalities

The Oral Glucose Tolerance Test (OGTT) is widely used to evaluate glucose abnormalities in thalassemia patients, though its reliability in TM is sometimes questioned due to hemoglobinopathy-related complications. Recent studies, such as those by Choudhary et al. (2013) (34,84) recommend continuous glucose monitoring (CGM) for more consistent tracking of glucose levels, particularly in TM patients at higher risk of diabetes (5,92). Additionally, Meloni et al. (2021) found that MRI-determined pancreatic iron levels correlated strongly with glucose metabolism outcomes, suggesting that pancreatic MRI may serve as a predictive measure for early intervention (84).

For TI, where glucose abnormalities are generally less severe, OGTT remains a useful diagnostic tool, though periodic CGM could capture subtle variations over time (86,92). The selective use of CGM and OGTT between TM and TI highlights the need for individualized diagnostic approaches, focusing on early detection and precise monitoring to guide treatment decisions effectively (92,93).

4.4. Chelation Therapy and Glucose Metabolism

Chelation therapy is a cornerstone of managing iron overload in thalassemia, with agents like deferoxamine, deferiprone, and deferasirox effectively reducing iron stores and mitigating glucose metabolism issues. Farmaki et al. (2011) (94). showed that combined deferoxamine and deferiprone therapy is particularly beneficial in TM, where higher iron loads necessitate aggressive chelation For TI patients, single-agent chelation based on liver iron levels offers effective management, avoiding the intensive regimens required by TM patients (59,68, 93).

Studies, such as those by Kontoghiorghe et al. (2016), (96) stress that early initiation and adjustment of chelation can prevent or delay the onset of diabetes in thalassemia by preserving pancreatic function, especially in high-risk TM cases. This demonstrates that chelation therapy's impact on glucose regulation varies significantly between TM and TI, reflecting different needs in intensity and timing of intervention (35,97).

4.5. Complications Related to Iron Overload

Iron overload-related Complications are more severe in TM than in TI, due to the higher transfusion frequency and resultant iron buildup. Common issues in TM include cardiac and hepatic complications and endocrine disorders, with cardiac siderosis being particularly concerned for its role in heart failure (96, 97,98). In TI, iron accumulation primarily affects the liver, with fewer cases of cardiac complications, although pulmonary hypertension and hepatic dysfunction are observed as the disease progresses (89, 20). Taher et al. (95,99) noted that the overall complication profile in TI warrants proactive but less intensive management (15).

Differences in complication rates and severity between TM and TI underscore the need for targeted monitoring and intervention strategies, with TM patients requiring frequent cardiac assessments, while TI patients benefit from liver-focused monitoring (9,45,100). This approach ensures that both TM and TI patients receive optimal care to prevent or manage their unique risk factors associated with iron overload.

4.6. Variability of Treatment Options

The management of glucose metabolism in thalassemia includes a wide range of treatment options, from dietary and exercise interventions to pharmacologic therapies like insulin and oral hypoglycemics. Nutrition and exercise play crucial roles, with diets high in fiber and low in simple carbohydrates aiding glucose control, particularly beneficial for TM patients prone to glucose intolerance. Tay et al. (2015) (86) highlight dietary interventions as effective in managing postprandial glucose levels, reducing the need for intensive pharmacological interventions (86).

Pharmacologic options vary between TM and TI. For TM, insulin therapy is often necessary due to more advanced glucose dysregulation, while oral hypoglycemics, such as glibenclamide, are used in milder cases or when lifestyle adjustments alone are insufficient (40,50,101). TI patients generally respond well to lifestyle modifications, often avoiding the need for medication, although regular monitoring remains essential (102). This spectrum of therapeutic approaches underscores the importance of customizing treatment based on thalassemia and individual metabolic status to optimize outcomes and quality of life. The glycemic monitoring strategies are summarized in figure 2.

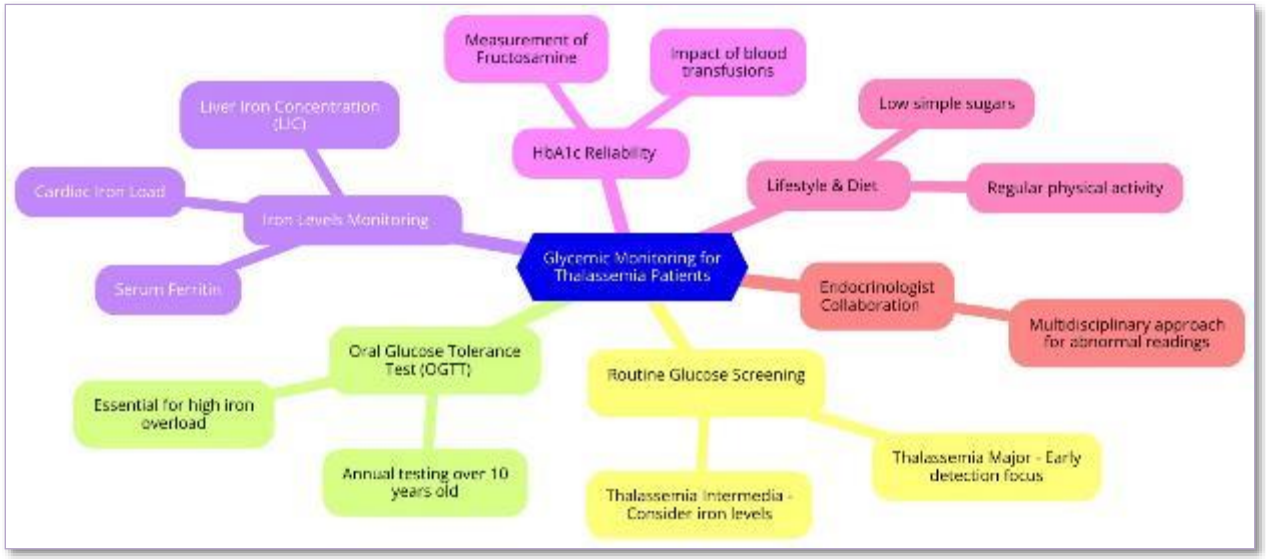

Figure 2 Glycemic Monitoring Strategies for Thalassemia Patients.

5. Conclusion

TM (TM) and TI(TI) exhibit distinct profiles regarding glycemic abnormalities, primarily due to differences in transfusion dependency and iron overload. TM patients, who require frequent transfusions, often experience significant iron accumulation in critical organs like the pancreas, liver, and heart, increasing their risk for glucose metabolism issues, including impaired glucose tolerance and diabetes. This iron overload impairs beta-cell function and contributes to insulin resistance, making TM patients particularly susceptible to diabetes. Conversely, TI patients, with less frequent transfusion requirements, accumulate iron more gradually, leading to fewer and generally milder glucose abnormalities. As a result, TI patients often manage glucose levels effectively with lifestyle modifications such as diet adjustments and regular exercise, while TM patients typically need more intensive glycemic management. (figure 1)

The difference in glycemic management between TM and TI highlights the need for tailored approaches. For TM patients, aggressive chelation therapy using agents like deferoxamine and deferiprone, along with regular glucose monitoring through oral glucose tolerance tests (OGTT) and continuous glucose monitoring (CGM), is essential to mitigate the effects of iron overload on pancreatic function. Pharmacological interventions, including insulin and oral hypoglycemics, are often necessary for advanced glycemic control in TM. In TI, less intensive chelation based on iron load allows for effective control without high intervention levels, with most patients achieving stable glucose levels through lifestyle interventions alone. Recognizing these distinct management needs ensures better patient outcomes and quality of life for those with TM and TI.

Recommendations (Figure 2)

Implement individualized therapy protocols based on transfusion frequency and organ-specific iron levels, with more aggressive chelation for TM (TM) patients to reduce the risk of iron-induced pancreatic dysfunction and subsequent diabetes.

Use fructosamine and fasting blood glucose (FBG) as regular monitoring tools, supplemented by an Oral Glucose Tolerance Test (OGTT) every 6–12 months for high-risk patients, and consider continuous glucose monitoring (CGM) if available to capture real-time glucose fluctuations for better glycemic management.

Emphasize lifestyle interventions, including tailored nutrition and structured exercise programs, particularly for TI(TI) patients, as these can support glucose stability, enhance overall metabolic health, and reduce the need for pharmacologic interventions, thus improving quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest, and all authors agree on the final manuscript and its publication.

Authors Contributions

All authors made significant contributions to this review. Ashraf Soliman and Vincenzo De Sanctis conceived the review's topic, guided the structure, and contributed to sections on glucose abnormalities and iron overload. Fawzia Alyafei helped design the comparative analysis framework, synthesizing literature on diagnostic and management strategies for TM and Intermedia. Shayma Ahmed focused on iron chelation therapies and metabolic impacts, drafting the results and discussion. Noora AlHumaidi reviewed diagnostic approaches, particularly the use of OGTT and CGM, and assisted in manuscript editing. Noor Hamed contributed recent insights on iron overload management and treatment efficacy. Ahmed Elawwa analyzed endocrine dysfunctions impacting glucose regulation, refining content on hormone imbalances. Nada Alaaraj examined age-related diabetes onset in thalassemia, aiding the discussion and clinical implications. Ahmed Khalil provided expertise on pharmacologic therapies and iron chelation, ensuring accuracy in the management strategy recommendations. All authors reviewed and approved the final manuscript, ensuring the review's accuracy and comprehensiveness.

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