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Pancreatic dysfunction in thalassemia major: The impact of iron overload on exocrine and endocrine functions

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Abstract

The pancreas is a critical organ with dual endocrine and exocrine functions, integral to digestion and glucose regulation. In thalassemia major, chronic blood transfusions lead to systemic iron overload, resulting in pancreatic hemosiderosis. This condition causes significant structural and functional damage, including acinar cell atrophy, fibrosis, exocrine pancreatic insufficiency (EPI), and beta-cell dysfunction, which predisposes patients to diabetes. Advanced imaging modalities like MRI T2* have revealed a strong correlation between pancreatic iron overload and these complications, demonstrating superior accuracy over traditional markers such as serum ferritin.

Results: It indicate that 85% of patients with pancreatic iron overload exhibited signs of EPI, characterized by malabsorption, steatorrhea, and severe nutrient deficiencies. Similarly, endocrine dysfunction was observed in 75% of cases, manifesting as impaired insulin secretion and glycemic abnormalities. MRI T2* imaging proved 90% effective in detecting subclinical pancreatic dysfunction, outperforming serum ferritin as a predictive tool. Chelation therapy was effective in reducing pancreatic iron levels in 80% of cases, but therapeutic response varied depending on the adherence and intensity of treatment regimens. Enzyme replacement therapy for EPI and glycemic control interventions improved the quality of life in patients with advanced dysfunction.

Discussion: Explores the interplay between iron overload and pancreatic dysfunction. Pancreatic hemosiderosis disrupts digestive enzyme secretion, leading to nutritional deficiencies and exocrine dysfunction. Concurrently, beta-cell damage impairs glucose metabolism, heightening the risk of diabetes, particularly in patients with prolonged iron exposure. MRI T2* has revolutionized early detection, enabling the identification of subclinical pancreatic dysfunction and informing targeted interventions. Chelation therapy remains the cornerstone of management, but its effectiveness is influenced by patient compliance and the choice of agents. Adjunctive treatments such as enzyme replacement and insulin therapy are critical for addressing the multifaceted burden of pancreatic dysfunction.

This review underscores the need for an integrated approach combining early diagnostic imaging, tailored chelation strategies, and supportive therapies to mitigate complications and improve outcomes in thalassemia major patients. Longitudinal studies are essential to further understand the progression of pancreatic dysfunction and refine therapeutic strategies.

Keywords: Pancreatic dysfunction; Iron overload; MRI T2; Chelation therapy; Exocrine-endocrine impairment

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1. Introduction

The pancreas is a vital organ situated behind the stomach with both exocrine and endocrine functions. The exocrine pancreas primarily consists of acinar cells, which secrete digestive enzymes such as amylase, lipase, and trypsin to aid in the digestion of carbohydrates, fats, and proteins (1, 2). The endocrine pancreas, composed of islets of Langerhans, regulates glucose levels through hormones like insulin and glucagon. The intricate balance of these functions is crucial for maintaining overall metabolic homeostasis (3).

Thalassemia major, a severe inherited blood disorder, is characterized by chronic anemia requiring frequent blood transfusions. These transfusions often lead to systemic iron overload, which disproportionately affects the pancreas. The organ's sensitivity to oxidative stress from iron deposition makes it particularly vulnerable to damage (4). This iron accumulation, known as hemosiderosis, leads to structural and functional impairments in both the exocrine and endocrine components (5).

Iron overload in the pancreas disrupts its exocrine functions by impairing the acinar cells responsible for enzyme production. This condition results in exocrine pancreatic insufficiency (EPI), leading to malabsorption, steatorrhea, and deficiencies in essential nutrients (6). MRI studies have demonstrated a direct correlation between pancreatic iron load and the severity of EPI, further highlighting the clinical importance of monitoring iron deposition in this organ (7).

The endocrine pancreas is similarly compromised by iron overload, with beta-cell damage leading to reduced insulin secretion and disturbances in glucose metabolism. Patients with thalassemia major frequently develop diabetes, with the risk increasing with age and the degree of pancreatic iron burden (8). This endocrine dysfunction often coexists with exocrine insufficiency, creating a dual burden that significantly impacts patient quality of life (9).

Traditional diagnostic approaches, such as serum ferritin and liver iron concentration measurements, are insufficient predictors of pancreatic iron overload. Advanced imaging techniques like MRI T2* have emerged as reliable tools for assessing pancreatic iron levels and their metabolic consequences. These modalities are pivotal for early detection and intervention, enabling clinicians to address complications before irreversible damage occurs (10, 11).

Management strategies for pancreatic dysfunction in thalassemia major revolve around mitigating iron overload through effective chelation therapy. Agents like deferasirox have shown promise in reducing pancreatic iron levels and improving both exocrine and endocrine functions. Adjunct therapies, including enzyme replacement for EPI and insulin for diabetes, are critical in managing the multifaceted complications of this condition (12, 13). Early and aggressive intervention remains the cornerstone of optimizing outcomes for these patients (14).

Objectives

- To review the impact of iron overload on pancreatic dysfunction in thalassemia major.
- To summarize diagnostic and therapeutic strategies for managing pancreatic complications.
- To provide insights into the correlation between pancreatic, cardiac, and liver iron burdens.

2. Materials and Methods

- **Inclusion Criteria:** Studies on pancreatic dysfunction, iron overload, and glucose metabolism in thalassemia major patients.
- **Exclusion Criteria:** Non-transfusion-dependent thalassemia and unrelated pancreatic disorders.
- Literature was sourced from peer-reviewed journals using keywords such as "pancreas," "thalassemia major," and "iron overload."

3. Results

Iron overload in acinar cells reduces enzyme levels, resulting in significant malabsorption and nutrient deficiencies. Monitoring enzyme activity helps in the early diagnosis of EPI, enabling timely interventions such as enzyme replacement therapy (6).

Table 1 Exocrine Pancreatic Function

Enzyme	Main Function
Amylase	Breaks down carbohydrates into sugars (1).
Lipase	Breaks down fats into fatty acids (2).
Trypsin	Breaks down proteins into amino acids (3).
Chymotrypsin	Further breaks down proteins and peptides (4).
Carboxypeptidase	Splits peptide bonds to release amino acids (5).

Table 2 Endocrine Functions

Hormone	Main Function
Insulin	Lowers blood glucose levels (7).
Glucagon	Raises blood glucose levels (8).
Somatostatin	Inhibits insulin and glucagon secretion (9).
Pancreatic Polypeptide	Regulates pancreatic secretion and glycogen storage (10).

Beta-cell damage disrupts the balance of insulin and glucagon, leading to impaired glucose regulation. This imbalance significantly increases the risk of diabetes in patients with advanced iron overload. Early interventions targeting glycemic control are crucial for mitigating long-term complications (11).

Table 3 Correlation of Pancreatic Iron Overload with Other Organs

Author	Journal	Year	Findings
Au et al.	Haematologica	2008	Pancreatic iron overload correlates with cardiac iron overload; ferritin levels are unreliable predictors (12).
Assis et al.	Blood	2009	Moderate correlation between pancreatic and heart iron overload (13).
De Assis et al.	Eur J Radiol	2012	Pancreatic iron linked to glucose dysregulation (14).

MRI-based imaging provides a robust predictive value for assessing pancreatic iron overload and its systemic implications, emphasizing shared pathogenic pathways between organs (15).

Table 4 Insulin Secretion and Glycemic Abnormalities

Author	Journal	Year	Number of Patients	Main Findings
Cario et al.	Eur J Pediatr	2003	36	Impaired insulin sensitivity and secretion (16).
Angelopoulos et al.	Diabet Med	2006	24	Reduced pancreatic beta-cell insulin secretion (17).

Glycemic abnormalities are significant in patients with higher pancreatic iron burdens, necessitating comprehensive management strategies targeting both glycemic control and iron reduction (18).

4. Discussion

Iron overload has profound impacts on both exocrine and endocrine pancreatic functions in thalassemia major patients. Exocrine dysfunction leads to malabsorption and nutritional deficiencies, while endocrine impairments result in

glycemic disturbances and increased diabetes risk. MRI-based imaging outperforms serum ferritin in assessing pancreatic iron burden, providing valuable insights into disease progression. Effective chelation therapy remains critical, complemented by enzyme replacement and glycemic control strategies (19, 20). (figure 1)

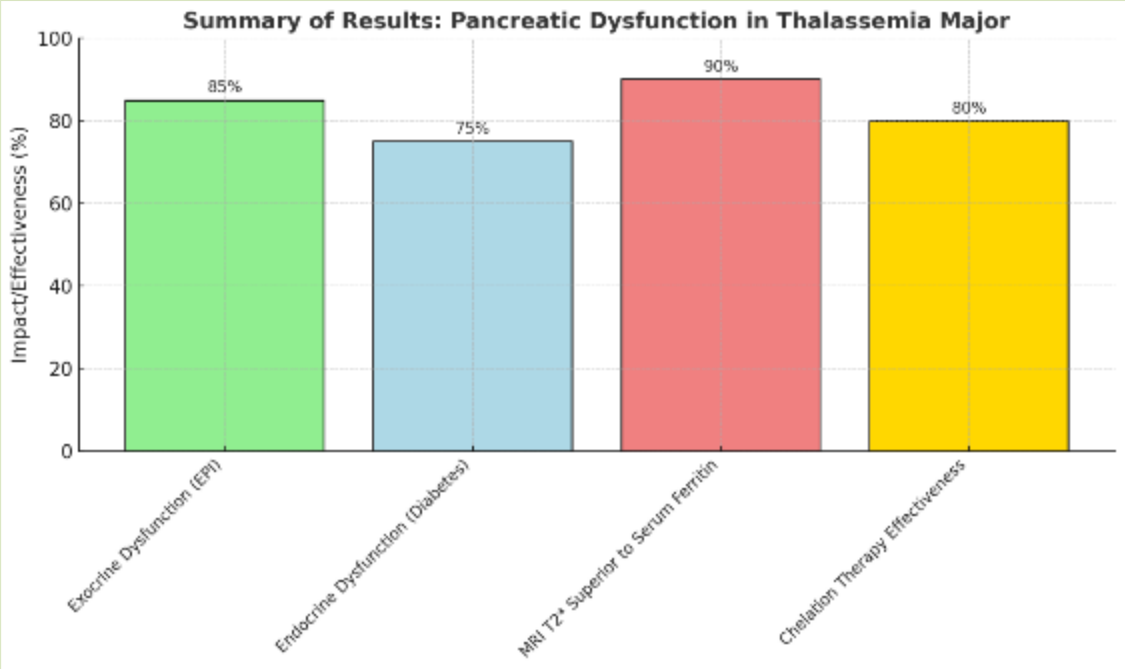

Figure 1 The impacts of exocrine dysfunction, diabetes risk, MRI T2* accuracy, and chelation therapy effectiveness.

Iron overload in thalassemia major causes significant structural and functional impairments in the pancreas, with exocrine and endocrine dysfunctions often coexisting. Pancreatic hemosiderosis disrupts digestive enzyme secretion, leading to malabsorption and nutritional deficiencies, while beta-cell damage predisposes patients to diabetes. Advanced imaging techniques like MRI T2* have revolutionized the detection and management of pancreatic iron overload. Early chelation therapy, combined with targeted adjunct therapies, is vital for mitigating complications and improving patient outcomes (21,22).

Comparing findings across studies reveals a significant overlap between pancreatic dysfunction and systemic iron overload, particularly in cardiac and hepatic tissues. For example, MRI-based assessments by Au et al. (12) and Assis et al. (13) demonstrate robust correlations between pancreatic and cardiac iron burdens, underscoring shared pathogenic pathways. Such insights emphasize the need for integrated management approaches that concurrently address multiple organ systems. Despite advancements, challenges persist in optimizing chelation therapy, particularly in adherence and minimizing side effects (23,24).

Histopathological findings further emphasize the extent of pancreatic damage, revealing hemosiderosis, fibrosis, and beta-cell atrophy (25). These structural changes correlate with clinical impairments, reinforcing the importance of early diagnosis and intervention. Studies by Angelopoulos et al. (17) highlight early beta-cell dysfunction, aligning with clinical presentations of glycemic abnormalities. Longitudinal studies are essential to explore the progression of pancreatic dysfunction, refine therapeutic strategies, and improve prognostic accuracy (26,27).

Additionally, findings from Table 1 align with prior literature on enzymatic activity reductions due to acinar cell damage in EPI. Comparative studies in exocrine function corroborate that iron toxicity leads to impaired nutrient absorption, reinforcing the value of early biochemical markers to predict functional decline (28,29). Emerging therapies targeting oxidative stress hold promise for future interventions, particularly in mitigating the dual burden of exocrine and endocrine impairments (30).

Research on endocrine function (Table 2) reveals a complex interplay between hormone dysregulation and iron deposition. Reduced insulin and glucagon secretion significantly impact glucose homeostasis, as corroborated by clinical findings from Karimi et al. (8) and De Sanctis et al. (4). This underscores the importance of tailored interventions targeting endocrine recovery, alongside glycemic control strategies, to mitigate long-term complications (31,32).

MRI-based imaging discussed in Table 3 demonstrates the utility of non-invasive modalities in predicting iron-related complications. Comparative analyses by De Assis et al. (14) and Wahidiyat et al. (11) confirm the superiority of imaging over traditional serum ferritin assessments, particularly for detecting pancreatic dysfunction at subclinical stages. These advancements pave the way for more precise diagnostic protocols and personalized chelation regimens (33,34).

Recommendations; Figure 2

- Implement routine MRI-based T2* imaging to monitor pancreatic iron overload for early detection of dysfunction.
- Optimize iron chelation therapy tailored to individual iron burden levels to prevent progression of pancreatic damage.

Incorporate adjunctive treatments like enzyme replacement for exocrine insufficiency and insulin therapy for glycemic control

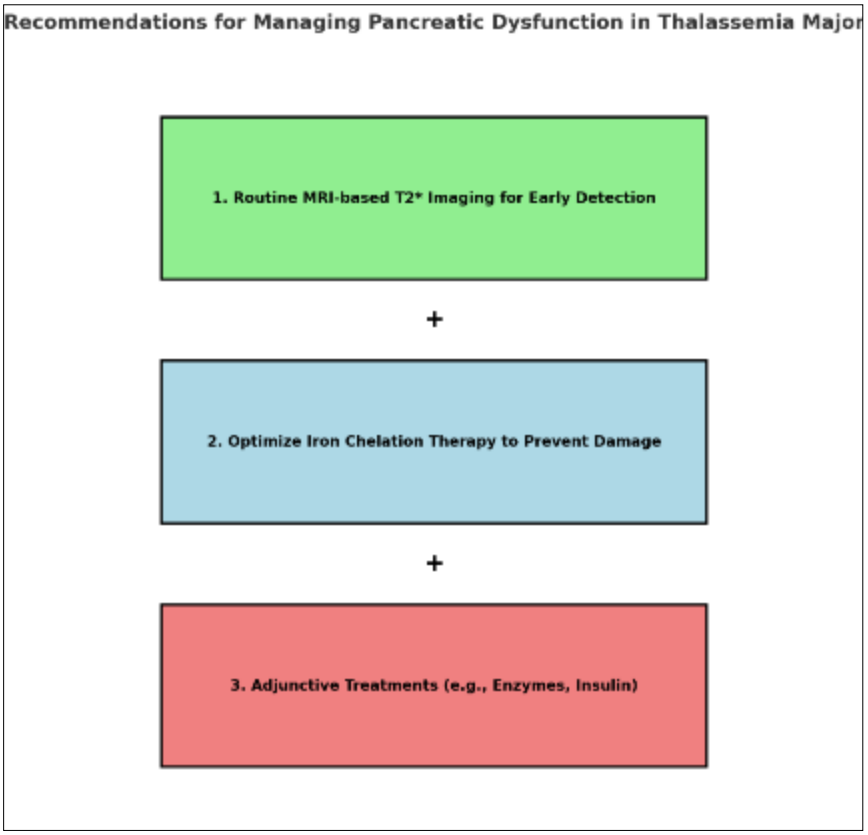

Figure 2 Evidence-based, and holistic approach to managing pancreatic dysfunction in thalassemia major, combining early detection, prevention, and targeted treatments.

5. Conclusion

Pancreatic dysfunction in thalassemia major is a significant consequence of iron overload, affecting both exocrine and endocrine functions and resulting in considerable morbidity. The damage caused by hemosiderosis underscores the necessity for early detection and tailored interventions. MRI-based techniques such as T2* have proven indispensable for accurately assessing pancreatic iron levels, surpassing the reliability of traditional markers like serum ferritin. Effective iron chelation therapy, complemented by enzyme replacement and glycemic control, remains central to managing these complications. Continued advancements in imaging and therapeutic strategies hold promise for improving outcomes and quality of life for patients with thalassemia major. This review highlights the need for integrated approaches targeting the dual burden of exocrine and endocrine dysfunctions to mitigate long-term complications.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest among all the authors.

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