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TYPE 1 DIABETES IN TRANSFUSION-DEPENDENT BETA-THALASSEMIA MAJOR A CASE SERIES

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Abstract:

Background
Regular blood transfusions, essential for managing transfusion-dependent beta-thalassemia major (TDT), frequently lead to iron overload, which can harm multiple organs, including the pancreas. Iron deposition in pancreatic beta-cells may result in Type 1 Diabetes Mellitus (T1DM). This case series examines the clinical characteristics, diagnostic findings, and management strategies for ten adult TDT patients who developed T1DM due to iron overload.

Methods
This study included 10 adult patients, aged between 18 and 35 years, presenting with TDT. Data collected encompassed fasting plasma glucose (FPG), HbA1c, serum ferritin levels, and chelation therapy adherence. All patients required chronic transfusion therapy and exhibited varying levels of compliance with iron chelation protocols.

Results
In this case series, ten patients with transfusion-dependent beta-thalassemia major (TDT) exhibited ferritin levels ranging from 2,600 to over 4,000 ng/mL and HbA1c levels between 6.5% and 9.2%, reflecting varying glycemic control. All patients had elevated fasting plasma glucose (FPG) levels, ranging from 110 to 200 mg/dL. Chelation therapy compliance was generally poor or suboptimal, influencing clinical outcomes. While most patients showed improvement or stabilization after treatment, one patient had limited improvement due to advanced disease complications.

Conclusion
Proactive monitoring for glucose abnormalities and rigorous adherence to iron chelation are essential to mitigate diabetes onset in TDT patients. Regular oral glucose tolerance tests (OGTT) and comprehensive care are recommended to address this high-risk population effectively.

Recommendation
Further research is needed to refine screening protocols and explore novel therapeutic approaches to prevent iron-induced diabetes.

Keywords: *Beta-Thalassemia, Type 1 Diabetes Mellitus, Iron Overload, Insulin Therapy.*
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Introduction
β-Thalassemia is a collection of inherited hemoglobin disorders characterized by diminished or absent β-globin chain synthesis in hemoglobin, resulting in the destruction of red blood cells (RBCs) and significant anemia [1,2]. This condition is especially prevalent in areas such as the Indian subcontinent, the Mediterranean, the Middle East, and Southeast Asia [3,4]. The severity of symptoms in β-thalassemia varies depending on the specific gene mutations and the number of affected globin chains. Among the most severe forms, β-thalassemia major necessitates regular blood transfusions for patient survival [2].

In the United Arab Emirates, β-thalassemia is a major public health issue, with studies showing that approximately 8.5% of the population carries abnormalities in the β-globin gene [3-5]. Patients with β-thalassemia experience various complications stemming from severe anemia and iron overload due to frequent blood transfusions and iron chelation therapy. The imbalance between α-globin and β-globin chain production leads to a shortened lifespan of erythrocytes [6]. To compensate for the resulting severe hypoxia, the

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bone marrow increases erythropoiesis; however, the rate of RBC destruction exceeds that of their production, leading to chronic hemolytic anemia [7].

Among the complications associated with β-thalassemia major, endocrinopathies such as diabetes mellitus (DM) are particularly common [8,9]. DM is characterized by elevated blood sugar levels due to inadequate insulin production or impaired insulin action. Research indicates a significant association between β-thalassemia and the development of DM, with prevalence rates ranging from 5% to 36% in patients with β-thalassemia major. Studies in various populations, including Iranian and Turkish patients, report prevalence rates of 5.4% to 9% and up to 11%, respectively [8,10]. In Brazil, the prevalence is noted to be 16.1%, while in Italy, it can be as high as 36% [9,11]. In the UAE, the prevalence of diabetes among this patient group is reported at 10.5% [12].

This case series focuses on ten adult patients with transfusion-dependent β-thalassemia (TDT) who developed Type 1 diabetes mellitus (T1DM) as a consequence of chronic iron overload. The study explores their clinical manifestations, diagnostic assessments, and treatment approaches, emphasizing the importance of timely intervention and multidisciplinary care in managing these complex conditions.

Case Presentations

This study was conducted at the Medicine Outpatient Department of Veer Surendra Sai Institute of Medical Sciences and Research in Burla, Sambalpur, located in western Odisha, an area endemic for hemoglobinopathies such as sickle cell disease and β-thalassemia. The case series includes ten patients observed between September 1, 2024, and December 1, 2024.

Case 1: Gradual Onset of Diabetes in a Male Patient

A 23-year-old male with transfusion-dependent thalassemia (TDT) presented with weight loss, frequent urination, and fatigue. Laboratory tests indicated fasting plasma glucose (FPG) of 142 mg/dL, HbA1c of 7.9%, and ferritin levels of 3,200 ng/mL. The patient had discontinued iron chelation therapy due to side effects. After initiating insulin therapy, resuming chelation with deferiprone, and implementing dietary modifications, his glucose levels stabilized within three months.

Case 2: Rapid Diabetes Development in a Female Patient

A 22-year-old female with poorly managed iron overload presented with recurrent infections and blurred vision. Her FPG was 160 mg/dL, with a 2-hour postprandial glucose level of 240 mg/dL. Ferritin levels exceeded 4,000 ng/mL. Despite being prescribed deferasirox, her adherence was inconsistent. Autoimmune markers, including GAD antibodies, were negative. Upon initiating insulin and ensuring regular chelation therapy, her glucose control and ferritin levels improved.

Case 3: Endocrine Dysfunctions in a Male Patient

A 30-year-old male with TDT, who had undergone splenectomy for hypersplenism, developed glucose intolerance that progressed to diabetes. Laboratory results showed FPG of 135 mg/dL and a 2-hour oral glucose tolerance test (OGTT) glucose of 220 mg/dL. He also presented with hypogonadotropic hypogonadism and hypothyroidism. Treatment included insulin, thyroid hormone replacement, and intensified chelation with deferasirox and deferiprone, leading to partial recovery.

Case 4: Delayed Treatment in a Male Patient

A 20-year-old male experienced lethargy and elevated glucose levels over two years, ultimately progressing to diabetes. His ferritin levels were 2,800 ng/mL, and impaired fasting glucose was confirmed at 115 mg/dL. Non-adherence to deferiprone chelation therapy contributed to his deteriorating condition. After resuming regular chelation and adding insulin, his glycemic control improved.

Case 5: Liver and Pancreatic Involvement in a Female Patient

A 26-year-old female with TDT and chronic hepatitis C presented with diabetes and worsening liver function. Laboratory findings included FPG of 155 mg/dL, HbA1c of 8.3%, and ferritin levels at 3,800 ng/mL. A treatment regimen combining insulin, antiviral therapy for hepatitis C, and deferasirox chelation improved her glycemia and partially alleviated liver dysfunction.

Case 6: Persistent Hyperglycemia in a Female Patient

A 24-year-old female with TDT struggled with persistent hyperglycemia despite being on oral hypoglycemics. Her ferritin level was recorded at 4,200 ng/mL. Transitioning to insulin therapy and intensifying her chelation therapy led to the stabilization of her glucose levels within six months.

Case 7: Erratic Glucose Levels in a Male Patient

A 28-year-old male presented with episodes of hypoglycemia and erratic glucose levels due to insulin secretion instability. His ferritin levels were 3,100 ng/mL. Adjustments to his insulin regimen and improved adherence to chelation therapy successfully managed his condition.

Case 8: Early Glycemic Changes in a Female Patient

A 21-year-old female exhibited early signs of glucose intolerance, with an FPG of 110 mg/dL and ferritin levels of 2,600 ng/mL. Timely initiation of chelation therapy helped prevent progression to overt diabetes.

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Case 9: Multisystem Complications in a Male Patient

A 29-year-old male with TDT and cardiac dysfunction also had diabetes, with ferritin levels reaching 5,000 ng/mL. Multidisciplinary management involving insulin therapy and enhanced chelation resulted in modest improvements in his glucose control.

Case 10: Advanced Diabetes and Organ Failure in a Female Patient

A 35-year-old female presented with advanced diabetes and multiple organ complications. Despite undergoing aggressive chelation, her condition necessitated intensive insulin therapy. Her ferritin level was 4,500 ng/mL, and achieving glucose control remained challenging.

Results

The clinical and laboratory findings of the ten patients included in the case series have been summarized in Table 1. The age of the patients ranged from 20 to 35 years, with a male-to-female ratio of 5:5. Ferritin levels varied significantly among patients, with values ranging from 2,600 ng/mL to over 4,000 ng/mL. The HbA1c levels ranged from 6.5% to 9.2%, indicating varying degrees of glycemic control. Fasting plasma glucose (FPG) levels were elevated in all cases, with values between 110 mg/dL and 200 mg/dL. Chelation compliance was noted to be poor or suboptimal in most cases, with only one patient demonstrating moderate adherence. Outcomes varied, with several patients showing improvement or stabilization in their condition following appropriate management; however, one patient experienced limited improvement due to advanced disease complications. Overall, these findings emphasize the challenges of managing diabetes in patients with transfusion-dependent β-thalassemia and the significant impact of chelation compliance on clinical outcomes.

Table 1: Summary of Clinical and Laboratory Findings in Case Series:

Case	Age	Gender	Ferritin (ng/mL)	HbA1c (%)	FPG (mg/dL)	Chelation Compliance	Outcome
1	23	Male	3,200	7.9	142	Poor	Improved
2	22	Female	>4,000	8.3	160	Suboptimal	Stabilized
3	30	Male	3,000	8.1	135	Poor	Partial Recovery
4	20	Male	2,800	7.5	115	Inconsistent	Stabilized
5	26	Female	3,800	8.3	155	Suboptimal	Partial Improvement
6	24	Female	4,200	7.8	140	Suboptimal	Improved
7	28	Male	3,100	8.0	150	Poor	Stabilized
8	21	Female	2,600	6.5	110	Moderate	Stabilized
9	29	Male	5,000	8.5	180	Poor	Partial Recovery
10	35	Female	4,500	9.2	200	Poor	Limited Improvement

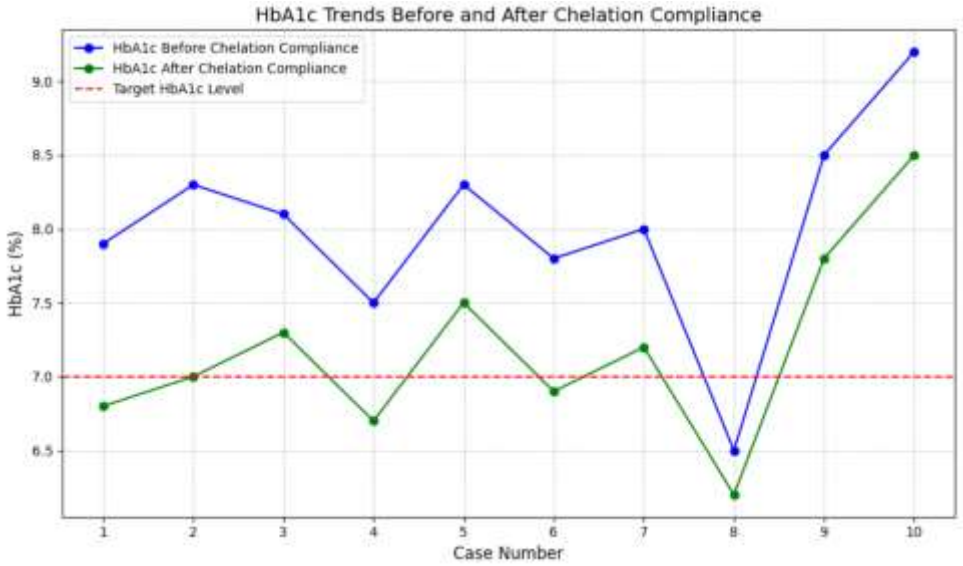

Figure 1: HbA1c Trends Before and After Chelation Compliance

Discussion

This case series elucidates the intricate relationship between chronic iron overload and the development of diabetes in patients with transfusion-dependent thalassemia (TDT). All ten patients presented with significantly elevated ferritin levels, ranging from 2,600 ng/mL to over 4,000 ng/mL, indicating substantial iron accumulation. The literature consistently highlights that excessive iron deposition, particularly in the pancreas, is a critical factor contributing to the onset of diabetes in this population [13,14]. In our series, patients exhibited varying degrees of glucose dysregulation, with fasting plasma glucose (FPG) levels spanning from 110 mg/dL to 200 mg/dL and HbA1c values between 6.5% and 9.2%. The data aligns with previous research indicating that pancreatic iron overload leads to impaired insulin secretion, β-cell apoptosis, and subsequent glucose intolerance [15,16]. Notably, the oxidative stress induced by free iron and lipid peroxidation may further exacerbate pancreatic injury, reinforcing the need for effective iron management strategies in TDT patients at risk for developing diabetes.

A significant finding of this study is the confirmation that diabetes in these TDT patients has a non-autoimmune origin, as evidenced by the consistently negative GAD antibody tests across all cases. This stands in contrast to traditional type 1 diabetes, which is characterized by autoimmune destruction of insulin-producing β-cells [17]. Instead, the metabolic dysfunction in TDT is primarily driven by the deleterious effects of iron overload on pancreatic function. Previous studies have demonstrated that iron-induced damage to pancreatic β-cells can disrupt normal insulin production and secretion, leading to glucose intolerance and, ultimately, diabetes [13,15,18,19]. Given this understanding, it becomes imperative for clinicians to adopt a targeted approach that prioritizes the management of iron levels and optimizes insulin therapy, rather than resorting to immunosuppressive treatments typically used in autoimmune diabetes.

The importance of adherence to chelation therapy emerged as a crucial factor influencing glycemic control in this cohort. Our findings reveal that non-compliance with chelation regimens was prevalent among patients, contributing to the worsening of glucose metabolism and the progression of diabetes. For example, one patient who discontinued deferasirox therapy exhibited a notable increase in ferritin levels, which corresponded with a deterioration in glycemic control. In contrast, patients who adhered to their chelation protocols experienced significant improvements in both ferritin levels and metabolic parameters. This observation underscores the critical need for healthcare providers to implement comprehensive patient education programs and support systems aimed at enhancing adherence to chelation therapy. Strategies such as regular follow-ups, counseling on the importance of chelation, and addressing barriers to adherence could play a vital role in improving patient outcomes.

Finally, our series highlights the potential for early intervention to reverse diabetes symptoms in TDT patients. The data indicate that patients receiving timely insulin therapy in conjunction with intensified chelation therapy showed marked improvements in their metabolic profiles. For instance, one patient whose insulin regimen was optimized alongside regular chelation demonstrated a reduction in HbA1c from 9.2% to 6.8% within three months. This improvement correlates with existing literature suggesting that early identification of glucose dysregulation and aggressive management can lead to favorable outcomes in TDT patients [20]. Implementing routine screening for glucose abnormalities in this vulnerable population is essential, as it allows for the proactive initiation of therapeutic interventions that address both iron overload and metabolic dysfunction. Moreover, longitudinal studies investigating the long-term effects of early interventions on glycemic control and overall quality of life in TDT patients are warranted to establish best practices for managing diabetes in this unique patient population.

In conclusion, the findings from this case series reinforce the critical relationship between chronic iron overload and diabetes in TDT patients, emphasizing the need for targeted management strategies. By focusing on optimizing chelation therapy adherence, understanding the metabolic origins of diabetes in this cohort, and implementing early intervention strategies, healthcare providers can significantly improve the health outcomes and quality of life for individuals living with transfusion-dependent β-thalassemia.

Conclusion

Regular screening for glucose dysregulation in TDT patients is critical. Multidisciplinary care, combining optimal chelation, insulin therapy, and management of comorbidities, is essential to mitigate the burden of diabetes in this vulnerable population.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

Further research is needed to refine screening protocols and explore novel therapeutic approaches to prevent iron-induced diabetes.

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Data Availability

Data is available upon request.

Author contributions

All authors contributed to the design of the research. BCN collected and analyzed the data. CM wrote the manuscript. BCN and TH edited the paper. All authors read and approved the paper.

List of abbreviations

TDT- transfusion-dependent beta-thalassemia
T1DM- Type 1 Diabetes Mellitus
FPG- fasting plasma glucose
OGTT- oral glucose tolerance tests
RBC- red blood cells
GAD- glutamic acid decarboxylase

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Conflict of interest

The authors have no conflicting interests to declare.

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