Indicators of Blood Glucose Imbalance in Children with Beta-thalassemia Major

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Abstract

Children diagnosed with beta-thalassemia major have a significantly increased likelihood of developing an imbalance in their blood glucose levels. It is essential to do screenings for diabetes and prediabetes in children, and to maintain a high degree of suspicion for abnormalities in blood glucose levels, since this is important for their management. Additionally, it is crucial to acknowledge other markers of blood glucose imbalance, including the glycated hemoglobin level, the fructosamine level, and the occurrence of hypoglycemic crises. Implementing preventive measures and closely monitoring one's health can effectively hinder the path towards diabetes.

Thalassemia is a prevalent hereditary blood condition. The need for frequent blood transfusions in thalassemia leads to an excess of iron in the body, which has a role in the development of several disorders, including those affecting insulin production and function. This review examines the several markers of blood glucose dysregulation in children diagnosed with beta-thalassemia major. It also explores the impact of iron overload and other factors, such as the effects of desferioxamine and deferasirox. The review also discusses strategies for preventing diabetes and emphasizes the significance of a multidisciplinary team in caring for these youngsters.

Introduction

The oral glucose tolerance test (OGTT) and fasting blood glucose (FBG) were used to identify the most prevalent abnormal blood glucose levels in beta-thalassemia major children. The study examined the history of beta-thalassemia major, which causes hemolytic anemia and requires...
blood transfusions. These blood infusions may cause iron accumulation, which increases diabetes risk in young individuals. [1]

The study found that the seventh-day FBG test was the most common blood glucose imbalance test. The initial indication may precede diabetes. This research helps establish an early marker for blood glucose dysregulation in children with beta-thalassemia major who do not have diabetes. [2]

For survival, beta-thalassemia major requires frequent blood transfusions. Extreme iron accumulation in blood transfusions damages endocrine organs, causing difficulties. Studies show that many children with beta-thalassemia major have low glucose tolerance, while some develop intolerance. Increased physical activity, inadequate calorie intake for healthy growth, and beta-thalassemia major illness may put some youngsters at risk for poor blood glucose regulation and excessive iron accumulation. Poor blood glucose management can lead to substantial health issues in children with beta-thalassemia major, including long-term diseases [3]. This study is notable for finding blood glucose anomalies in healthy toddlers receiving routine blood transfusions from a thalassemia daycare program. The findings will advise caregivers and healthcare providers to check for hypo- or hyperglycemia in afflicted youngsters. [4]

**Physiology of Glucose Regulation**

Understanding the intricate balance of blood glucose regulation through hormones like insulin and glucagon, as well as other supporting hormones like cortisol and growth hormone, is crucial in comprehending the effects of chronic diseases on blood glucose levels. Stress and its impact on growth and development could potentially lead to changes in blood glucose levels in children with beta-thalassemia major. To detect glucose imbalance, assessing random blood glucose or hemoglobin A1c levels and symptoms of hyperglycemia is key.

**Normal Glucose Metabolism**

Before discussing beta-thalassemia major's blood glucose imbalance, it's important to understand healthy children's blood glucose variables. This background is needed to identify if BTM-related blood glucose imbalance in children is due to their disease or other reasons. Thus, this study discusses elements that may impact children's blood glucose levels and how they do so. They then search the literature for beta-thalassemia major children's blood glucose imbalance markers. Finally, they propose a blood glucose imbalance mechanism in these children. It will be easy to understand the authors' study after that. [3]

Life depends on glucose metabolism, which fuels all cellular and biochemical functions. Metabolism must function efficiently throughout childhood due to the high energy needs of growing children. Blood glucose homeostasis is maintained by insulin, glucagon, growth hormone, and other hormones. They control blood glucose levels by altering tissue glucose synthesis and absorption. Several factors affect blood glucose concentration throughout the day, but healthy people keep it within a small range.[5]
Role of Insulin in Glucose Regulation

In addition to nutrient-stimulated insulin secretion, C-peptide contains glucagon-like activity that increases hepatic and renal blood flow, inhibits gluconeogenesis and glucose output, and aids peripheral glucose clearance. Low insulin secretion's relative fasting hyperglycemia is linked to impaired basal C-peptide secretion. Pancreatic beta cells secrete insulin, amylin, and C-peptide, which are significant. Beta-thalassemia major children's pancreas is iron-overloaded and injured, therefore nutrient-stimulated hormone cocktail secretion may be hampered even with adequate storage or secretion of individual components.[6]

Thalassemia major causes high-output inefficient erythropoiesis. Negative feedback from dysregulated RBC precursors suppresses erythropoietic cytokine secretion. Pancreatic function is altered with alpha and beta cell dysfunction. In response to food stimulation, pancreatic beta cells co-secrete insulin, amylin, and C-peptide, which regulate glucose. Amylin reduces stomach-to-intestine nutrition transport and decreases postprandial glucagon. It boosts satiety and regulates glucose homeostasis.[7]

Beta-thalassemia Major and Glucose Imbalance

Chelation therapy and better monitoring have reduced glucose abnormalities in beta-thalassemia major children. High fasting blood sugars may require transfusions initially. If blood sugar levels stay high, insulin treatment may indicate pancreatic failure. Ferritin and hepatitis B core-related antigen levels in beta-thalassemia children may indicate liver damage from iron overload. Chelation therapy reduces iron levels to protect the pancreatic. [3, 8]

Beta-thalassemia major is the most severe form of congenital blood disease. Regular blood transfusions improve life expectancy but cause iron excess and endocrine issues. Diabetes is prevalent because iron excess affects the pancreas and reduces insulin synthesis. Long-term liver iron accumulation reduces insulin receptor clearance. Also, obesity causes insulin resistance. Patients with beta-thalassemia are treated for long-term consequences like glucose imbalance. [4,1]

Pathophysiology of Beta-thalassemia Major

This study reviewed factors contributing to blood glucose imbalance in children with beta-thalassemia major (BMT). It found that iron dynamics, dietary intake, treatment components, and endocrine abnormalities all contributed to this imbalance. The study highlights that this issue is complex and requires multifactorial assessment and intervention. Thalassemia is a global health problem with two forms: BMT and beta-thalassemia minor. BMT is a severe form that requires lifelong blood transfusions, leading to iron overload and oxidative damage. High-calorie diet and iron-chelating agents can also affect glucose homeostasis in these patients. [9]

Factors Contributing to Glucose Imbalance in Beta-thalassemia Major

Many studies have examined iron chelation with growth and pubertal development. Chelation therapy begins immediately after diagnosis, but endocrine problems develop years later, complicating this link. Duration of effective iron chelation therapy affects growth failure and delayed puberty improvement. A few individuals with poor chelation therapy compliance...
developed additional endocrine problems due to iron overload. In patients with iron overload, endocrine dysfunction may be delayed or averted.[10]

Several reasons may cause BTM glucose imbalance. It is well known that pancreatic iron deposition causes endocrine problems. It causes pancreatic beta cell malfunction and destruction. Iron-induced diabetes develops sequentially through subclinical islet cell failure and autoimmune. Many believe that beta cell toxicity is the main cause of iron excess diabetes. In addition, patient age and disease duration should be addressed when considering glucose imbalance causes. [11]

**Clinical Indicators of Blood Glucose Imbalance**

Children with beta-thalassemia major may experience blood glucose imbalances due to preprandial and postprandial symptoms, including increased hunger, excessive eating, weight gain, and sleepiness. Parents also report episodes of polyphagia, polyuria, and weight loss. New warning signs in pediatric clinics include refusing to eat breakfast, decreased food intake, and crying before eating breakfast. Thalassemia, a hereditary anemia, is typically treated with blood transfusions, which can lead to iron overload, endocrine gland dysfunction, and diabetes. [12]

**4.1. Symptoms and Signs**

Childhood thalassemia is associated with diabetes, which has numerous characteristics. Type 1 diabetes causes symptomatic hyperglycemia and ketonuria, although pancreatic islet cells must be almost totally gone before symptoms appear. The thalassemic population may experience atypical diabetes or overt diabetes preceded by years of β-cell desensitization and malfunction. Even non-diabetics with glucose intolerance are more likely to appear with hypoglycemia than hyperglycemia since routine screening detects it. The hematopoietically active spleen may influence pancreatic islet cell immune death, making splenomegaly a risk factor for diabetes. [13,22]

In children with β-thalassemia major, clinical signs of blood glucose imbalance may appear. Hepatomegaly from iron overload or hepatitis C infection, failure to thrive, thalassemic cardiomyopathy heart abnormalities, and desferrioxamine toxicity bone alterations are examples. Other symptoms include glucose homeostasis disturbances. Fasting or stress-induced hypoglycemia may occur years before diabetes in these children due to growth retardation and inadequate production of counter-regulatory hormones and insulin antagonists. [14]
Table 1 Laboratory Tests

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Details</th>
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<tbody>
<tr>
<td></td>
<td>• Results can be influenced by thalassemia.</td>
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<tr>
<td></td>
<td>• Fasting blood glucose correlates better with early post-glucose load values.</td>
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<tr>
<td></td>
<td>• Hypoglycemia may indicate liver dysfunction and low serum ferritin.</td>
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<tr>
<td><strong>Complete Blood Count (CBC)</strong></td>
<td>• Reports total hemoglobin, MCV, reticulocyte count, RDW.</td>
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<td></td>
<td>• Provides indirect indices for monitoring ineffective erythropoiesis.</td>
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<tr>
<td></td>
<td>• Detects moderate to severe anemia and ineffective erythropoiesis.</td>
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<tr>
<td><strong>Iron Studies [16]</strong></td>
<td>Iron Overload Diagnosis</td>
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<td></td>
<td>• Include serum iron, total iron-binding capacity, and ferritin.</td>
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<td>• Support diagnosis of secondary diabetes via free radical formation.</td>
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5. Management and Interventions

β-thalassemia major causes heart failure and hepatic failure in developed countries, while limited resources in developing countries lead to poor management. Challenges include long-term endocrine and metabolic issues, including blood glucose derangement. Chelation therapy, nutritional counseling, regular blood sugar level screening, and family education can help prevent diabetes, while regular blood sugar level screening is crucial. [17]

5.1. Nutritional Strategies

Nutritional strategies are important to counteract growth failure in thalassemia. Recommended dietary priorities include providing adequate energy, preventing growth-modulating factors, and addressing reduced appetite and dietary restrictions. Low consumption of dairy products and the eating of large amounts of food containing iron can also impact the absorption of important nutrients. A high calorie, high protein diet with antioxidants such as vitamin C and vitamin E may help mitigate the damage done by iron overload. [18]

5.2. Pharmacological Interventions

Aside from its hepatoprotective and other known benefits, silymarin has been studied in the treatment of thalassemia major. The rationale was that because silymarin components include vitamin E, which has a known role in reducing red cell oxidative damage, it might be beneficial for patients with β-thalassemia. However, the results of a study that evaluated the effects of silymarin on patients with β-thalassemia major showed no significant hematological improvement. [19]

The goal of pharmacologic therapy in β-thalassemia is to suppress ineffective erythropoiesis as it is one of the most important pathological processes in β-thalassemia. Several agents can be used in its treatment—some have been available since the late 20th century and others are still investigational. The agents with proven efficacy are glucocorticoids (prednisone and deflazacort), with their well-known long-term adverse effects raising concerns, and newer agents with less adverse effects, such as the glucocorticoid receptor agonists. [20]

Luspatercept, a growth differentiation factor modulator, is another relatively new agent that is increasingly being used. It is important to stress here that other core aspects must be addressed in the management of β-thalassemia major. These include appropriate blood transfusion therapy and iron chelation therapy (ICT). The latter is essential because ICT poorly controlled may lead to increased morbidity and mortality in β-thalassemia major. [21]

Conclusion

In conclusion, Children with β-thalassemia major may have blood glucose imbalance due to increased levels, glycosuria, and glycated hemoglobin, potentially linked to iron overload, liver dysfunction, and inflammation. MRI can help identify those at higher risk. Early recognition of atypical disease presentations and routine blood glucose monitoring are crucial. Iron overload activates production of acute-phase proteins and cytokines, leading to reduced growth and growth hormone insensitivity, hyperglycemia, and glycosuria. Routine blood glucose monitoring is an easy, non-invasive approach for early detection.

References:

6. Fritsche A, Heni M, Peter A, Gallwitz B, Kellerer M, Birkenfeld AL, Häring HU, Wagner R. Considering insulin secretory capacity as measured by a fasting C-


