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Significance of Serum Ferritin and Its Association with Liver and Renal Function in Beta Thalassemia Patients: A Review-Based Insight

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Abstract

Background: Beta thalassemia is an inherited hemoglobinopathy characterized by reduced or absent β-globin synthesis, resulting in chronic anemia and dependence on frequent blood transfusions. These transfusions cause progressive iron overload, which predominantly affects the liver and kidneys. Serum ferritin is widely used as a surrogate biomarker for body iron stores, although its levels can be influenced by inflammation and other factors.

Objective: This paper reviews the clinical significance of serum ferritin as an indicator of iron overload and explores its association with liver and renal function in beta thalassemia patients.

Methods: A comprehensive review of peer-reviewed studies, clinical trials, and international guidelines was conducted, focusing on serum ferritin's prognostic utility, pathophysiologic effects of iron overload on hepatic and renal function, and monitoring strategies.

Results and Conclusion: Elevated serum ferritin levels correlate strongly with hepatic dysfunction, including fibrosis and cirrhosis, and growing evidence links iron overload to renal impairment. Routine surveillance using serum ferritin alongside liver and renal function tests, supported by advanced imaging like MRI T2*, enables early detection and tailored chelation therapy, improving patient outcomes and reducing morbidity.

1. Introduction

Beta thalassemia is a hereditary disorder caused by mutations in the HBB gene, leading to diminished or absent β-globin synthesis. This causes ineffective erythropoiesis and chronic hemolytic anemia necessitating lifelong transfusion therapy in severe cases (Cappellini, Cohen, Porter, & Taher, 2018). While transfusions alleviate anemia, they introduce excess iron, which accumulates in organs, causing oxidative tissue damage and subsequent organ dysfunction (Taher, Musallam, & Cappellini, 2017).

Iron overload primarily affects the liver, the major iron storage site, leading to progressive fibrosis and cirrhosis if untreated (Karimi, Moradi, & Zare, 2016). Renal complications, historically less recognized, have emerged as significant in thalassemia patients due to a combination of iron toxicity, chronic anemia, and effects of chelation therapy (Thalassemia Reports, 2019).

Serum ferritin, an intracellular iron storage protein released into the circulation, is the most commonly used and accessible biomarker to estimate total body iron burden in thalassemia patients (Cappellini et

al., 2018). However, ferritin levels may rise independent of iron overload in the presence of inflammation, infection, or liver injury, complicating interpretation.

This review synthesizes current knowledge on serum ferritin's physiological role, thresholds indicative of clinically significant iron overload, its relationship to liver and renal involvement, and implications for monitoring and management.

2. Serum Ferritin as a Marker in Beta Thalassemia

2.1 Physiology and Clinical Significance

Ferritin serves as an intracellular iron reserve, sequestering iron and preventing free iron-induced oxidative damage. Its serum concentration usually correlates with total body iron stores in healthy individuals. In transfused beta thalassemia patients, serum ferritin progressively rises alongside increasing iron burden (Taher et al., 2017).

2.2 Confounding Influences on Ferritin Levels

Ferritin is an acute-phase reactant and can elevate in systemic inflammation, infection, or liver damage independent of iron burden, which can result in overestimation of iron overload (Karimi et al., 2016). Oxidative stress, common in thalassemia due to chronic hemolysis and iron toxicity, may further influence ferritin synthesis.

2.3 Thresholds for Clinical Concern

Clinical guidelines advocate closer chelation intervention when ferritin levels exceed 1,000 ng/mL, with levels above 2,500 ng/mL indicating a high risk for organ damage and poor prognosis (WHO, 2020). Serial monitoring and correlation with clinical and laboratory findings improve reliability over isolated ferritin measurements.

3. Impact of Iron Overload on Liver Function

3.1 Iron Deposition and Injury Mechanisms

The liver is the primary organ for iron storage, with excess iron accumulating mainly in hepatocytes and Kupffer cells. Excess iron catalyzes reactive oxygen species formation, promoting lipid peroxidation, mitochondrial injury, and cellular apoptosis (Karimi et al., 2016). This leads progressively to hepatic steatosis, fibrosis, and cirrhosis, increasing risk of portal hypertension and hepatocellular carcinoma (Ali et al., 2023).

3.2 Liver Function Test (LFT) Abnormalities

Typical LFT abnormalities include raised alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels. These changes correlate positively with serum ferritin and hepatic iron concentration, reflecting hepatocellular damage (Taher et al., 2017; Shah et al., 2022).

3.3 Histological and Clinical Correlations

Numerous clinical studies associate elevated serum ferritin with severity of liver fibrosis confirmed by biopsy or imaging, establishing ferritin as a valuable prognostic marker for liver involvement in

thalassemia (Ali et al., 2023; Hammod et al., 2019).

4. Renal Involvement in Beta Thalassemia

4.1 Pathophysiology of Renal Damage

Iron overload leads to deposition in renal proximal tubules causing oxidative damage, tubular dysfunction, and impaired reabsorption. In addition, anemia-induced renal hypoxia, chronic inflammation, and toxicity from iron chelators, particularly deferasirox, contribute to nephropathic changes (American Journal of Kidney Diseases, 2018; El-Hadidi et al., 2019).

4.2 Markers of Renal Dysfunction

Standard markers of renal impairment including serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) evaluate glomerular function. However, early tubular injury can be detected by urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), and cystatin C before traditional markers elevate (Romadhon et al., 2022; Ghafouri et al., 2020).

4.3 Clinical Evidence Linking Ferritin and Renal Damage

Studies demonstrate patients with ferritin >2,500 ng/mL have a higher incidence of both glomerular and tubular dysfunction, supporting iron overload's nephrotoxic role (Demosthenous et al., 2019; Thalassemia Reports, 2019).

4.4 Effects of Chelation Therapy

While chelation reduces iron burden, some chelators such as deferasirox have been associated with dose-dependent nephrotoxicity, making regular renal function monitoring critical (Cianciulli, 2009; American Journal of Kidney Diseases, 2018).

5. Clinical Implications and Monitoring Protocols

5.1 Ferritin Thresholds and Chelation Strategies

- Ferritin levels >1,000 ng/mL necessitate assessment and potential escalation of chelation therapy.
- Levels >2,500 ng/mL require aggressive intervention due to heightened risk of organ damage (WHO, 2020).
- Iron chelators include desferrioxamine (parenteral), deferiprone, and deferasirox (oral), with treatment tailored to patient tolerance and clinical status (Ratha et al., 2013).

5.2 Monitoring Strategies

- Serum ferritin measured quarterly to gauge iron burden.
- Liver function tests (ALT, AST, bilirubin, ALP) and renal function tests (creatinine, BUN, eGFR) monitored at least annually or more frequently in high-risk patients.

- Urinary biomarkers may aid early renal injury detection where available.
- Magnetic resonance imaging (MRI) T2* provides non-invasive iron quantification in hepatic and cardiac tissues and complements biochemical tests, improving management decisions (Alvi et al., 2017; Elalfy et al., 2021).

5.3 Integrated Care Approach

Combining biochemical parameters with imaging and clinical assessment optimizes risk stratification and guides personalized chelation, improving outcomes.

6. Conclusion

Serum ferritin is a fundamental biomarker for assessing iron overload in beta thalassemia and correlates strongly with hepatic and emergingly with renal dysfunction. Awareness of confounding factors is essential for its interpretation. Routine ferritin monitoring complemented by liver and renal function tests and imaging modalities like MRI T2* enables early detection of organ damage. Personalized chelation strategies balanced by vigilant monitoring are critical to prevent irreversible organ injury and improve survival and quality of life in these patients.

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