

Short Note

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Zeal Soni , Samkit Vora , [Dev Desai](#) *

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Short Note

Insights on Ferritin as a Screening and a Diagnostic Marker for Still's Disease: A Narrative review

Zeal Soni, Samkit Vora and Dev Desai *

Smt. NHLMMC, Ahmedabad, India; rlzs040@gmail.com (Z.S.); samkit11.vora@gmail.com (S.V.)

* Correspondence: devhdesai01@gmail.com

Abstract: Still's disease, also known as systemic juvenile idiopathic arthritis, is an autoimmune disorder with a triad of fever, salmon pink rash, and inflammatory polyarthritis. Its diagnosis is quite challenging due to the lack of specific symptoms and overlap with many other rheumatological and autoimmune disorders. However, recent studies have shown that high serum ferritin levels can act as a biomarker for this disease. Ferritin is an intracellular iron storage protein that acts as a pro-inflammatory reactant. There are various explanations indicating the presence of higher ferritin levels in Still's disease. High ferritin tells us about disease severity, and prognosis and can also predict life-threatening complications that can be easily prevented and thus it helps in reducing mortality associated with Still's disease. However, there are certain limitations to the use of ferritin as the only diagnostic marker for Still's disease. Overcoming those limitations can take the diagnosis of Still's disease to a higher level.

Keywords: still's disease; ferritin; arthritis

Main body:

Still's disease is a rare autoimmune disorder that is characterized by a triad of evanescent salmon-pink maculopapular rash, inflammatory arthritis, and quotidian spiking fever (which means daily recurring fever with temperature returning to normal in between symptoms) (1). The rash can be aggravated by heat (after hot showers) and by rubbing the skin (known as the Koebner phenomenon). Other symptoms include myalgia, inflammatory myopathies, sore throat, lymphadenopathy, splenomegaly, and serositis. However, the frequency of symptoms and disease course vary from person to person. It has three patterns: self-limited disease, intermittent flares, and chronic disease. The etiology of this disorder is unknown but may be triggered by a viral or bacterial infection or a toxin. Both genetics and environmental factors play an important role in its pathogenesis. It usually affects 16-45 years age group. It is a form of systemic juvenile idiopathic arthritis that paradoxically affects adults and not children. It is also associated with neutrophilic leukocytosis and anemia of chronic disease which is characterized by low iron, TIBC, transferrin saturation, and high ferritin levels (2). Due to ongoing inflammation in the body, there are high levels of ESR and CRP found along with abnormal liver function tests and negative antinuclear antigen and rheumatoid factor.

The diagnosis of Still's disease is difficult as there are no specific markers and tests available and because of the overlapping symptoms with other disorders, especially rheumatoid arthritis. It is a diagnosis of exclusion (3). However, there are various studies done which indicate an association between high serum ferritin levels and Still's disease. The diagnostic criteria performed by Yamaguchi et al 1992 are the most sensitive. Thus, elevated serum ferritin along with raised inflammatory markers and low glycosylated ferritin can act as a diagnostic marker for Still's disease (4).

Treatment of this disorder is also non-specific and includes NSAIDs, corticosteroids, DMARDs, and other immunosuppressants which are given based on disease severity. It has been found that the ferritin levels reduce once treatment for Still's disease is started.

Ferritin is a storage protein for iron present in every cell of the body. Ferritin is highly expressed in cells like macrophages, hepatocytes, and reticuloendothelial cells of the body. It makes the iron

available for various cellular processes while also preventing excess iron concentration within the cells. Free iron acts as a catalyst for free radical formation via the Fenton reaction and thus is toxic for cells. Apoferritin binds to the ferrous form of iron and stores it in ferric form, which makes it non-toxic for the cell. Ferritin accumulation within cells forms hemosiderin. Iron is less available in the hemosiderin form compared to the ferritin form. Under normal circumstances, ferritin levels directly correlate with the total body iron stores. Therefore, serum ferritin level is the most accurate test to evaluate iron stores in the body. Serum ferritin also acts as a positive acute phase reactant which means its levels increase during infections, malignancy, and autoimmune conditions like rheumatoid arthritis, thyroid disorders, hemochromatosis, Still's disease, etc. (5). On the other hand, its levels decrease in iron deficiency anemia. Expression of ferritin levels is regulated by cytokines, oxidative stress, hypoxia, thyroid and growth hormones, and lipopolysaccharides found in Gram-negative bacteria. Overall, ferritin can act as a pro-inflammatory marker and an immunosuppressant.

There are two isoforms of ferritin: H (heavy) and L (light). H forms are found in low iron content organs like the heart and pancreas. These have multiple catalytic sites and their functions are iron detoxification, intracellular iron transport, and immunomodulatory effects. On the other hand, L forms are found in the liver, spleen, and other organs with high iron content; these forms are released in circulation. The L forms have the function of iron nucleation, mineralization, and long-term storage. H forms are present in higher concentrations in Still's disease (6).

The concept of hyperferritinemia has emerged recently in explaining the pathophysiology of certain disorders like adult-onset Still's disease, Antiphospholipid syndrome, septic shock, etc. (7). It states that ferritin aggravates the inflammation present within the body in such diseases and leads to complications. In Still's disease, macrophage activation causes hyperferritinemia. However, this hyperferritinemia in Still's disease can be explained via different mechanisms as illustrated in many researches. The normal value of serum ferritin ranges between 40-200 ng/ml. Levels above 1000 ng/ml have been found in Still's disease. The following are the mechanisms (8):

(1) HEME OXYGENASE 1 ENZYME:

Heme oxygenase 1 enzyme is expressed by macrophages and endothelial cells during stressful conditions like infections, and inflammatory and autoimmune conditions. This enzyme is associated with ferritin expression. It has been found that there are high levels of HO-1 mRNA in Still's disease, this demonstrates that hyperferritinemia is seen in this disorder.

(2) CYTOKINES:

Cytokines like IL-1B, IL-6, and TNF alpha induce ferritin synthesis. In autoimmune disorders, cytokine levels increase due to inflammation which would further increase ferritin levels.

(3) NITRIC OXIDE SYNTHESIS:

Cytokines also indirectly affect ferritin levels by inducing nitric oxide synthesis. Nitric oxide activates iron regulatory proteins (IRP) 1 and 2, which play a role in ferritin production, and this in turn results in higher ferritin levels.

(4) FERRITIN GLYCOSYLATION:

Glycosylation of ferritin prevents its degradation by proteolytic enzymes. Studies have shown that patients with Still's disease have low glycosylation levels thus reducing ferritin degradation and in turn causing high ferritin levels. The diagnosis of Still's disease is a diagnosis of exclusion, various criteria have been developed for its diagnosis. One of the criteria developed by the American College of Rheumatology and Fautrel et al included the level of the glycosylation ferritin $\leq 20\%$ as a major criterion for diagnosis (9)

Serum ferritin levels are used to assess the following in Still's disease:

- The severity of the disease = higher the levels, more the severity and risk of complications.
- The prognosis of life-threatening complications like macrophage activation syndrome = high ferritin level is suggestive of poor prognosis.
- Monitoring of disease activity = its levels are found to be decreased in remission, while patients with active disease have higher levels.

Despite various studies showing high ferritin levels in Still's disease, it cannot be used as a sole marker for diagnosis due to various reasons. The most important reason is the lack of a standardized cutoff value for ferritin. Some studies show that the levels should be more than 1000 ng/ml while others suggest ferritin levels to be above 3000 ng/ml for diagnosis. The lack of a standardized threshold makes it harder to diagnose this disorder (10) Another reason is the non-specificity of the test. Serum ferritin levels are elevated in many other conditions like hemochromatosis, amyloidosis, and other inflammatory conditions. Lastly, there are variations found within patients. Many patients with Still's disease are asymptomatic or have atypical presentation which makes the diagnosis more challenging. Also, the genetics of every patient is difficult and since we don't know the exact pathogenesis of the disease, we cannot use ferritin as the only marker for diagnosis of Still's disease.

Conclusion:

In conclusion, it can be said that serum ferritin level plays a valuable role in diagnosing Still's disease. Hyperferritinemia in Still's disease drives the disease pathogenesis and adds further to inflammation in the body. Since the diagnostic criteria for Still's disease are not clear, some researchers have included glycosylated ferritin as a major criterion for diagnosing this disorder. The use of ferritin to assess the disease severity, predict its complications, and know the disease prognosis can help in making a proper treatment plan for the patient and thus help in preventing associated mortality. Thus, serum ferritin levels along with other inflammatory markers like ESR and CRP can aid in the diagnosis of Still's disease. However, the lack of a standardized threshold, presence of confounders, variation in disease progression, fluctuations in symptoms, and non-specificity of the test are some of the pitfalls that can cause a delay in diagnosis and must be addressed further.

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