Clinical Significance of Ferritin Measurement in Patients with Different Stages of Rheumatoid Arthritis

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Received: 10.05.2015
Accepted: 01.06.2015
Med Con June 2015 Vol 10, No 2, 23-26

Abstract

Background: Serum ferritin is generally considered the best clinical measure of body iron stores. Over the last few years, accumulating data have implicated a role for ferritin as a signaling molecule and direct mediator of the immune system. Serum ferritin has recently been observed to be elevated in various autoimmune diseases.

Objectives: To evaluate serum ferritin in blood samples from patients with different stages of rheumatoid arthritis (RA) before treatment and to investigate the relationship to clinical outcome.

Materials and methods: The study was carried out before therapy, in a group of 41 patients with different stages of RA, ranging in age between 28-65 years. The serum values of ferritin were evaluated in a group of 24 controls presenting no signs of rheumatic disease. The serum ferritin levels were measured by ELISA. Data were reported as means ±SD with 95% confidence limits. The statistical significance of difference was determined with Student’s t-test. Prevalence was compared by the χ² test. Fisher’s exact test and linear regression were used. Correlation analyses were performed by means of Pearson test.

Results: Serum ferritin was significantly higher in RA (levels are age and gender dependent). In patients with different stages of RA, before treatment, the increase of serum ferritin levels were significant (ranges from 57.14 ng/mL-145.17 ng/mL, mean value 129.4±10.5 ng/mL) vs. normal controls’ (ranges from 41.45-55.76 ng/mL, mean value 51.3±4.7 ng/mL; p<0.01). Seventeen (40%) patients with signs of inflammation (C-reactive protein 60.16±4.86 mg/L, range 46.14 to 84.18 mg/L) had a significantly (p<0.01) higher serum ferritin level. This was mainly due to the increased oxidative stress and to the extinction of the inflammatory process. Three (7%) patients with RA had hyperferritinemia that did not correlate with elevated titers of rheumatoid factor or anti-cyclic citrullinated peptide antibodies.

Conclusion: In RA, there was a significant correlation between serum ferritin, C-reactive protein and erythrocyte sedimentation rate. Serum ferritin is associated with the systemic inflammatory activity of RA. Serum ferritin was the superior indicator for disease status.

Keywords: rheumatoid arthritis, ferritin, disease severity

Introduction

Rheumatoid arthritis (RA) is a chronic, recurrent joint disorder, with a poorly understood pathogenesis [1]. Symptoms and severity of RA vary from person to
person and can change from day to day [2]. Rheumatoid arthritis tends to begin slowly with minor symptoms that come and go, usually on both sides of the body, and progress over a period of weeks or months. Bouts of disease activity are called flare-ups, while inactive periods are called remission [3,4].

Ferritin is known to be a pro-inflammatory mediator inducing expression of pro-inflammatory molecules, yet it has opposing actions as a pro-inflammatory and as an immunosuppressant. Ferritin is a serum predictor of iron storage. Serum ferritin appears to be a particularly sensitive index of iron status when stores are low [5].

High levels of serum ferritin have been associated with malignant disease and tissue damage. Hyperferritinemia has been rarely investigated in autoimmune diseases. Factors that affect prognosis include rheumatoid factor, age at time of diagnosis, overall health, and whether complications have developed [6].

At present, no single test of disease activity in RA is effective because RA may cause various kinds of symptoms and signs. The DAS28 score is used extensively to evaluate disease activity in patients with RA. DAS28 is a composite index that provides clinicians with a simple and objective assessment of the patient’s level of disease activity and progression [7,8].

### Material and Methods

**Study group**

This study involved patients with RA diagnosed according to the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association). Serum ferritin levels were determined in 41 untreated patients (28 women and 13 men), with different stages of RA (aged 53.76±14.2 years, age range 28-65, mean of arthritis duration 12.4±7.6 years). All patients fulfilled the American College of Rheumatology criteria for RA. Serum ferritin levels were measured by ELISA. The second group was of 30 patients in remission.

**Control group**

Serum ferritin levels were determined in 24 healthy subjects (19 women and 5 men, aged 34.9±7.7 years, age range 27-54).

**Statistical analysis**

Data were summarized as mean value (x)±SD. The statistical significance of difference was determined with Student’s t-test. Prevalence was compared by the χ² test. Fisher’s exact test and linear regression were used. Correlation analyses were performed by means of Pearson test.

### Results

Disease activity was assessed using the DAS28 score. Rheumatoid arthritis is a chronic disease, but the disease activity is a fluctuating process, showing great variation even during the course of one day as well as longer time periods.

Serum ferritin levels correlated with conventional clinical and laboratory indices of disease activity such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Significant associations were observed between ferritin and CRP and duration of morning stiffness. No difference was observed between men and women.

In patients with active RA, the serum levels of ferritin were significantly higher (129.4±10.5 ng/mL, ranges from 57.14-145.17 ng/mL) as compared to those of the control group (51.3±4.7 ng/mL, ranges from 41.45-55.76 ng/mL) (p<0.01) (Figure 1).

In 30 patients with RA in remission, the serum levels of ferritin were significantly higher (72.7±8.2 ng/mL, ranges from 38.45-87.76 ng/mL) as compared to controls (p<0.01) (Figure 2).
mL, ranges 43.35 to 95.27 ng/mL) as compared to those of the control group (51.3±4.7 ng/mL, ranges from 41.45-55.76 ng/mL) (p<0.01) (Figure 2).

There was a significant correlation between ferritin (129.4±10.5 ng/mL, range 57.14 ng/mL to 145.17 ng/mL), and morning stiffness duration (r=0.478; p=0.026). Serum ferritin levels also correlated positively with that of CRP (60.16±4.86 mg/L, range 46.14 to 84.18 mg/L) (r=0.613, p<0.01).

Ferritin was found to be higher in serum of patients with RA and the level correlated with the disease activity and joint destruction. No significant correlation was present between ferritin level and disease duration.

Three (7%) patients with RA had hyperferritinemia that did not correlate with elevated titers of rheumatoid factor or anti-cyclic citrullinated peptide antibodies.

**Discussion**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may have a high impact on patients’ quality of life as it is associated with disability, morbidity and an increased mortality rate. Rheumatoid arthritis is a chronic, systemic inflammatory disorder that primarily affects joints [9]. It may result in deformed and painful joints, which can lead to loss of function. Studies at molecular/genetic levels continue to explore various biomolecules as potential markers of the disease [10].

Ferritin has been implicated in various diseases and may be important in autoimmune conditions. Serum ferritin levels (acute phase reactant) were measured in patients with RA and the correlations of these parameters with the disease activity score (DAS28) were investigated. Ferritin is a protein in the body that is used to store iron [11].

The ferritin blood test can detect elevated or low levels of ferritin in the body, which may indicate disease such as hemochromatosis, RA, certain cancers, anaemia, or iron deficiency. The expression of ferritin is under delicate control and is regulated at both the transcriptional and post-transcriptional levels by iron, cytokines (tumour necrosis factor-alpha and interleukin-1α), hormones, and oxidative stress [12].

The immunological actions of ferritin include binding to T lymphocytes, suppression of the delayed-type hypersensitivity, suppression of antibody production by B lymphocytes, and decreased phagocytosis of granulocytes [13].

The ferritin test measures the amount of iron stored in the body. Iron, an essential element for many important cellular functions in all living organisms, can catalyse the formation of potentially toxic free radicals [14]. Excessive iron is sequestered by ferritin in a nontoxic and readily available form in a cell. Ferritin is composed of 24 subunits of different proportions of two functionally distinct subunits: ferritin H and L. Serum ferritin concentration as an index of storage iron in RA. Any inflammatory disorder can raise the ferritin level [15].

Serum ferritin level is a marker of body iron stores and may be an indicator of iron deficiency in patients with chronic inflammation such as RA [13]. The present findings agree with a previous report of high serum ferritin levels in RA patients compared to healthy controls [16]. Thus, serum ferritin is an index of iron stores also in RA. In active disease, higher than expected values of serum ferritin are probably due to a shifting of iron from the circulating pool to the reticuloendothelial cells of the synovial membrane [17].

Hyperferritinemia is associated with inflammation, infections and malignancies [18]. High concentrations of ferritin are found in the synovial fluid of RA patients, and in patients with juvenile RA correlates with disease activity [19]. Serum ferritin was shown to be a significant predictor of disease severity [20, 21].

Further investigation into the mechanisms of ferritin in RA group is warranted.

**Conclusion**

The serum ferritin concentration may provide a useful indication of reduced body iron stores in patients with RA. Hyperferritinemia in RA correlates with disease activity. This study indicates that serum ferritin, among the various RA tests, is the most useful biochemical marker for evaluating the disease activity of patients with RA. Our study related to severity and prognosis of RA demonstrated that serum ferritin was a significant predictor of destruction of articular cartilage of joints. Further studies with large samples need to be done to confirm findings.

*All authors have read and approved the final manuscript.*

**References**