ORIGINAL RESEARCH

Serum Ferritin: A Biomarker of Disease Activity in Lupus Nephritis

Kripasindhu Gantait[1], Akhsaya Elango[2]

Abstract

Background: Lupus nephritis being the prime etiology of mortality in SLE patients not only alters the course of the disease but also causes exacerbation. So in search for a feasible and accessible biomarker, this study aims to determine the importance of serum ferritin as a surrogate of disease activity in lupus nephritis patients.

Materials and methods: Number of SLE patients with and without lupus nephritis is 20 each; diagnosis was made based on SLICC criteria, enrolled in our study. They are subjected to SLEDAI-2k and rSLEDAI scores. Based on rSLEDAI score, SLE patients were categorized into group I, 20 SLE patients with lupus nephritis, and group II, 20 SLE patients without nephritis. Serum levels of ferritin were assessed by chemiluminescent immunoassay (CLIA). Biochemical and immunological tests were done, and the results were analyzed and correlated.

Results: Group I exhibited higher but not statistically significant serum ferritin levels compared to group II ($p = 0.07$). Ferritin levels were also observed to have significant positive correlation with rSLEDAI scores ($p < 0.01$, $r = 0.6$), SLEDAI scores ($p < 0.001$, $r = 0.7$), and anti-ds DNA antibody levels ($p = 0.013$, $r = 0.4$).

Conclusion: Serum ferritin is a promising, widely available and useful biomarker of disease activity in lupus nephritis.

Keywords: Ferritin, Lupus nephritis, SLEDAI, SLEDAI-2k.

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Introduction

Systemic lupus erythematosus (SLE) is immune complex-mediated condition. SLE is a multigenic disease. The described prevalence of SLE varies from 20 to 140 per 1,00,000,[1] while the Indian value is 3.2 per 1,00,000.[2] Since SLE has been hypothesized as a disease of urbanization and technological advancement, there has been an increasing trend of SLE over time.[2,3]

Despite low prevalence, the 5-year survival rate of SLE in India was rated the poorest in the world. Advanced renal failure causes death in most patients of SLE.[3,4] The renal manifestation of SLE considerably alters the course of the disease.

Ferritin, an iron storage protein, is critical for iron homeostasis.[5] In recent years, ferritin being used as an inflammatory marker has been the subject of extensive reviews.[6] It has been established that moderate levels of ferritin are associated with active SLE, rheumatoid arthritis, multiple sclerosis, and catastrophic antiphospholipid syndrome and may play a role in dermatomyositis.[7,8]

Several studies carried over different ethnic populations across the world support the association between high levels of serum ferritin and disease activity of SLE.[9–12] In this study, we compare the serum ferritin levels in lupus nephritis patients to SLE patients without nephritis and we determine the utility of serum ferritin as a biomarker of disease activity in lupus nephritis patients.

Materials and Methods

The study was conducted in the rheumatology unit of Midnapore Medical College, West Midnapore, West Bengal, from June 2020 to December 2020. The study protocol was approved by the Institutional Ethics Committee of Midnapore Medical College. Patients ($n = 40$) who fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria[13] were enrolled in our study. Patients with infection, bleeding, pregnancy, diabetes mellitus, and iron-deficiency anemia were excluded from the study. SLEDAI-2k (range 0–105)[14] and rSLEDAI, respectively, were utilized for disease activity. rSLEDAI is defined as the sum of the SLEDAI-2ks accrued in the renal domain of the measure (range 0–16).[15]

Patients in the cross-sectional study are categorized into *group I:* 20 SLE patients with lupus nephritis—rSLEDAI score more than or equal to 4 ($n = 18$) or biopsy-proven lupus nephritis in the past ($n = 2$). *Group II:* 20 SLE patients without nephritis—rSLEDAI score of 0 ($n = 20$). After a detailed clinical history and examination, blood samples were collected for hematological, biochemical, and immunological tests. Renal biopsy was done only for SLE patients with lupus nephritis. The serum levels of ferritin were quantified by chemiluminescence immunoassay (CLIA).

Statistical Analysis

This study's data were coded and analyzed using the Statistical Package SPSS version 28. Data were summarized using mean, standard deviation, median, minimum, and maximum in

[1,2]Department of Medicine, Midnapore Medical College, Midnapore, West Bengal, India

Corresponding Author: Kripasindhu Gantait, Department of Medicine, Midnapore Medical College, Midnapore, West Bengal, India, Phone: +91 9434243054, e-mail: drkripa2000@gmail.com

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quantitative data and using frequency for categorical data. The mean serum level of ferritin in group I and group II was compared by Student's *t*-test. Correlation of serum ferritin with SLEDAI and rSLEDAI scores and anti-ds DNA were analyzed by Pearson's correlation and Spearman's correlation test. *p*-values <0.05 were considered as statistically significant.

Result

The mean age of the 20 lupus nephritis was 31.75 ± 4.25 (18–46 years) with 20 SLE without nephritis (40.20 ± 4.48; 26–55 years). Among the 40 participants, 35 were female and 5 were males.

Normal serum ferritin levels were taken as 28–365 ng/mL in males and 5–148 ng/mL in females. The mean serum ferritin levels of group I and group II were compared by Student's *t*-test as shown in Figure 1. We infer that the mean serum ferritin is higher though not statistically significant in group I compared to group II ($p = 0.07$).

Active disease was defined as SLEDAI ≥8 and scores less than 8 was considered inactive. There were 16 active cases in group I and 12 active cases in group II.

All patients ($n = 40$) were subjected to correlational analysis. From the scatterplots shown in Figure 2 where dots represent individual samples, we infer from the uphill pattern that there is a significant positive and linear correlation between serum ferritin and rSLEDAI scores (p <0.01, $r = 0.6$). Serum ferritin was also observed to have a significant positive correlation with SLEDAI-2k scores as shown in Figure 3 (p <0.001, $r = 0.7$).

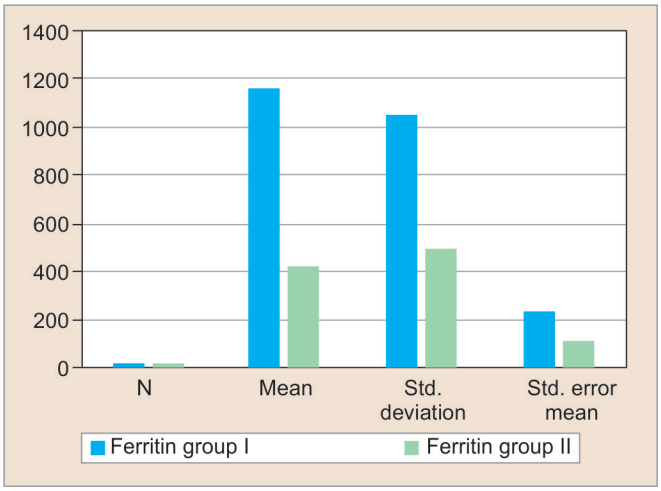

Fig. 1: Comparison of serum ferritin of group I and group II

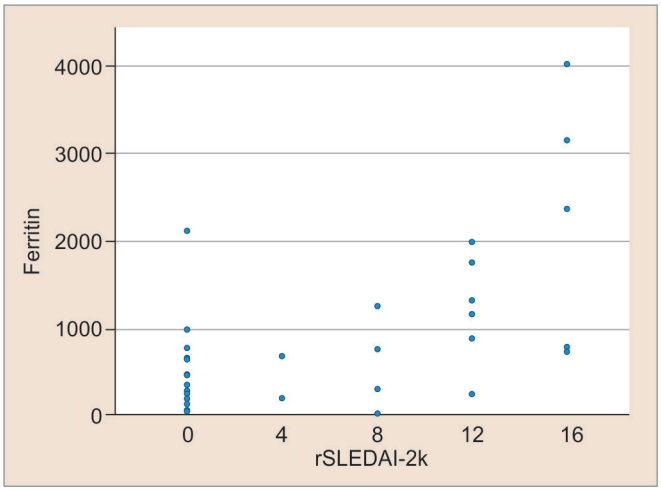

Fig. 2: Scatter plot of ferritin by rSLEDAI

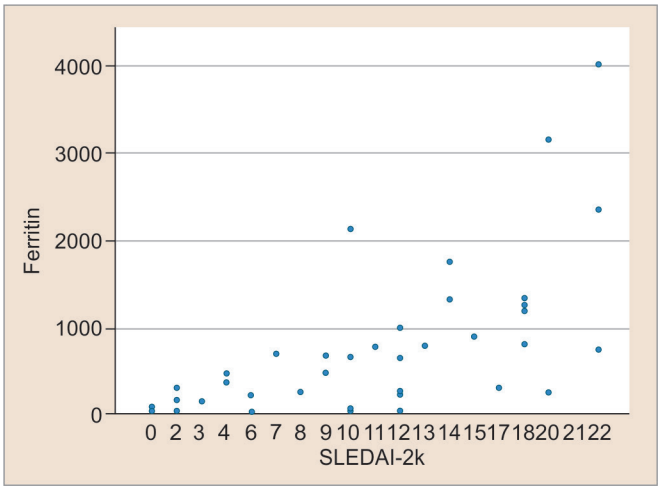

Fig. 3: Scatter plot of ferritin by SLEDAI

Table 1: Correlation of ferritin with other parameters

Parameters	*Serum ferritin*
Serum creatinine	$p = 0.144$
C-reactive protein	$p = 0.253$
Erythrocyte sedimentation rate	$p = 0.063$
Anti-ds DNA	$p = 0.013$
C3	$p = 0.464$
C4	$p = 0.13$

Serum ferritin was also compared with other laboratory parameters like serum creatinine, CRP, ESR, anti-ds DNA, C3, and C4, and the results are tabulated in Table 1. From Table 1, serum ferritin was observed to have significant positive association with anti-ds DNA levels ($p = 0.013$, $r = 0.4$).

Discussion

This current study proves the positive correlation between higher levels of serum ferritin with SLEDAI scores. This was in harmony with the study of Nishiya et al.,[9] Lim et al.,[10] Beyan et al.,[11] and Tripathy et al.[12] However, this finding is in disharmony with the results of Hesselink et al. stating that ferritin levels can be normal despite high disease activity.[16] But the sample size of this study is small.

In our study, serum ferritin was observed to have positive correlation with rSLEDAI scores and anti-ds DNA levels. Patients with lupus nephritis exhibited higher though not statistically significant serum ferritin levels compared to SLE patients without renal involvement, corroborating the results of Tripathy et al.[12]

It has been put forward as a novel concept that endogenous nucleic acids activate dendritic cells, mesangial cells, and macrophages to produce abundant inflammatory cytokines and IFN-α and IFN-β.[17–20] There is accumulating evidence of IFN-α as a central cytokine mediator of inflammation in SLE. Many studies support the specific role for IFN-α in the synthesis or secretion of

ferritin.[21,22] Thus, increased ferritin levels can be explained in lupus nephritis patients.

In our study, we conclude that in the midst of plethora of markers of lupus nephritis which has been extensively researched, ferritin may be considered as a promising and more accessible biomarker of disease activity in lupus nephritis. Further studies on its reliability and predictive potential are mandated.

Orcid

Kripasindhu Gantait https://orcid.org/0000-0001-8484-5489

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