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C-reactive protein and serum iron: Exploring the link between inflammation and iron metabolism

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ABSTRACT

Aim: This study aimed to examine the link between C-reactive protein (CRP), serum iron, and hematological indices in a cohort from a Saudi hospital, with a focus on inflammation-induced hypoferremia.

Methods: A retrospective cross sectional study was carried out involving 2478 patients attending a tertiary care hospital in Saudi Arabia during the period January 2023 through December 2024. C-reaction are protein serum, iron and hematological indices were measured by immunoturbidimetric and colorimetric methods.

Results: There was a marked negative correlation between CRP and serum iron concentration. As CRP levels increased, serum iron concentration decreased significantly, with a mean serum iron concentration of 14.2 µmol/L in the high CRP group, compared to 21.5 µmol/L in the low CRP group ($p < 0.01$). Notably, CRP emerged as an independent variable correlated with serum iron levels, emphasizing its role in inflammation-induced changes in iron metabolism. The other correlation with serum ferritin and red cell distribution width is also in accordance to the impact of inflammation on hematological indices. There were differences in serum iron between genders, but the correlation between CRP and serum iron level was consistent in both genders.

Conclusion: This research highlights the role of chronic inflammation in hypoferremia and emphasizes the significance of CRP as a key marker of inflammation, which impacts iron metabolism. The findings have implications in explaining the aspects of anemia of chronic disease (ACD) and underline the need for integrating markers of inflammation in the assessment and management of Anemia. Further studies are needed to explore novel therapeutic approaches targeting hepcidin and cytokine pathways.

Keywords: C-reactive protein, iron, inflammation, iron metabolism

INTRODUCTION

Inflammation is a hallmark of many acute and chronic diseases, often accompanied by elevated levels of C-reactive protein (CRP).[1] This compound is produced in response to inflammation and is associated with iron metabolism and hematological parameters.[1,2] In anemia of chronic disease, iron metabolism is often disrupted due to inflammation, a condition closely linked to this type of anemia[3] So these associations are helpful in the diagnosis and management of anemia or inflammatory disorder.[1,3]

This research aims to illustrate the relationship of CRP, serum iron and other hematological parameters in a Saudi hospital cohort and observe its effect at a systemic level. Inflammation triggers the secretion of cytokines, which alter the distribution and utilization of iron in the body.[2,4] CRP is a direct marker of inflammation and has been linked with changes in serum iron levels. This relationship is particularly seen in anemia of chronic diseases where inflammation promotes the retention of iron in macrophages, thus lessening the amount that can be used for erythropoiesis.[5,6] This explains why individuals with chronic inflammation often exhibit anemia profiles. This means that even when the stores of iron are sufficient or are larger than usual, the serum iron levels remain low.

Specific characteristics within the Saudi population may influence the prevalence and presentation of anemia and inflammatory disorders, in the Eastern province of the country which was surveyed, anemia was found out to have reached up to a 35.5% prevalence rate, whereas another study from Jazan recorded this number as being even larger, up to 67.35%, disparities such as these highlight the need for targeted research in order to grasp the complexities regarding inflammation, iron metabolism, and blood indicators.[7-10]

Hepcidin, a key polypeptide hormone, regulates iron homeostasis by mediating the sequestration of iron during inflammation, thereby disrupting normal iron processing.[6] Further disrupting the metabolic equilibrium and blood cell formation within the body. The interplay of all the aforementioned factors leads to the development of anemia for those with chronic inflammatory diseases within Eastern Saudi Arabia. Considering the targeting of therapeutic techniques focusing on chronic diseases with anemia as the consequence, the regulation of polymorphisms within the hepcidin gene should be taken into account.[10-13] Previous studies have highlighted the role of CRP as a marker of inflammation and its impact on iron metabolism. However, limited research has explored this relationship in Saudi Arabia, where unique population characteristics, including dietary habits and genetic polymorphisms, may influence outcomes. This study aims to investigate the relationship between CRP, serum iron, and hematological parameters, focusing on how inflammation influences iron metabolism, particularly in the Saudi population

MATERIALS AND METHODS

Study design and population

This retrospective cross-sectional study analyzed data from 2,478 patients who presented to a tertiary care hospital in Saudi Arabia between January 2023 and December 2024. Inclusion criteria encompassed patients aged 18 years and older with documented CRP levels, serum iron measurements, and complete hematological indices. Patients with missing or incomplete data, as well as those with known hematological disorders (e.g., thalassemia, sickle cell anemia) or recent blood transfusions within the past three months, were excluded to minimize confounding factors.

Data collection

Patient data were retrieved from electronic medical records to assess clinical and laboratory parameters. CRP levels were measured to assess systemic inflammation. The levels of this protein were measured in milligrams per liter, mg/L using a high sensitivity immunoturbidimetric assay. Iron status indicators included serum iron (measured in μmol/L using a colorimetric method), total iron-binding capacity (TIBC), and transferrin saturation (TSAT), calculated as (Serum Iron / TIBC) × 100. Serum ferritin levels, an acute-phase reactant, were also analyzed to assess iron stores, with adjustments made for inflammatory status during the analysis. Hematological indices included hemoglobin (HGB) in g/dL, red blood cell count (RBC; $\times 10^{12}$/L), mean corpuscular volume (MCV) in femtoliters (fL), platelet count (PLT; $\times 10^{9}$/L), and red cell distribution width (RDW), which were used to assess erythrocyte morphology and

anisocytosis. Demographic data, including age, gender, nationality, and relevant clinical history, were also collected to provide broader context for the findings. All laboratory assays, including CRP and serum iron measurements, were performed using automated systems. The CRP levels were analyzed using a high-sensitivity immunoturbidimetric assay (Cobas c702, Roche Diagnostics, Germany).

Statistical analysis

Data were analyzed using GraphPad Prism version 10.1.0. Descriptive statistics summarized patient demographics and laboratory values. Continuous variables are described using the mean and standard deviation (SD) or the median and interquartile range (IQR), depending on the distribution of the data. Categorical variables are summarized as counts and percentages.

Normality of data distribution was evaluated using the Shapiro-Wilk test. For normally distributed variables, independent t-tests compared means between groups; for non-normally distributed variables, the Mann-Whitney U test was employed. ANOVA with post-hoc Tukey analysis evaluated differences across multiple groups.

Correlations between CRP, serum iron, and hematological indices were assessed using Pearson's correlation coefficient for parametric data and Spearman's rank correlation for non-parametric data. Multivariate linear regression models identified independent predictors of serum iron levels, adjusting for potential confounders such as age, gender, and CRP levels.

To further explore the impact of inflammation on iron metabolism, patients were stratified into subgroups based on CRP levels, low CRP group ≤10 mg/L and high CRP group >10 mg/L. Comparisons of serum iron levels and hematological indices between these subgroups were conducted to assess the effect of systemic inflammation. Statistical significance was defined as a two-tailed p-value < 0.05. Data visualization, including scatter plots and box plots, was performed using the Matplotlib and Seaborn libraries to illustrate relationships between variables.

Ethical approval for the study was obtained from the Institutional Review Board of the Research Ethical Committee of the Institutional Review Board of King Fahad Hospital in Al-Ahsa, Ministry of Health, Kingdom of Saudi Arabia (No. 42-EP-2024), ensuring compliance with the Declaration of Helsinki. Patient confidentiality was maintained by anonymizing data during analysis.

RESULTS

The following table includes demographic data and study variables, and the study sample consisted of 2,478 patients with a mean age of 45.3 years. Out of the total subjects, 1,217 were men, and 261 were women. The results showed that the mean serum CRP level was 12.5 mg/L (± 5.3), with a range of 0.1 mg/L to 80 mg/L. The mean serum iron concentration in males was 18.2 μmol/L (± 4.7), ranging from 5 to 35 μmol/L, while in females, it was 17.9 μmol/L (± 4.9), with a range of 4 to 34 μmol/L Other hematological parameters, such as HGB, RBC, MCV, and PLT, aligned with the descriptive statistics shown in Table 1.

The correlation analysis provided in Table 2 illustrates the CRP and serum iron data in relation to other hematological parameters. A weak negative relationship ($r = -0.23$, $p < 0.05$) between CRP and serum iron, suggests that an increase in CRP concentration results from a decrease in serum iron concentration. On the other hand, CRP and platelet count readings had a weak negative correlation ($r = -0.28$, $p < 0.05$). A moderate positive correlation was observed between serum iron and mean corpuscular volume (MCV) ($r = 0.31$, $p < 0.05$), indicating increased red cell volume with higher serum iron levels. The ratio of hemoglobin content to RBC count also had a strong inverse correlation ($r = -0.74$, $p < 0.01$). Although these parameters were within low to normal ranges, they highlight the compensatory mechanisms seen in states of iron deficiency.

Table 1: Descriptive Statistics of the Study Cohort

Parameter	Mean ± SD	Range
Age (years)	45.3 ± 16.8	18 – 90
CRP (mg/L)	12.5 ± 5.3	0.1 – 80
Serum Iron (µmol/L)	18.2 ± 4.7	5 – 35
Hemoglobin (g/dL)	13.5 ± 1.8	8 – 17
RBC Count ($\times 10^{12}$/L)	4.8 ± 0.6	3.5 – 6.5
MCV (fL)	85 ± 6	70 – 100
Platelet Count ($\times 10^{9}$/L)	250 ± 75	100 – 450

Table 2: Pearson's Correlation Coefficients Between CRP, Serum Iron, and Hematological Indices

Parameter 1	Parameter 2	Correlation Coefficient (r)	p-value
CRP	Serum Iron	-0.23	<0.05
CRP	Platelet Count	-0.28	<0.05
Serum Iron	MCV	0.31	<0.05
Hemoglobin	RBC count	0.74	<0.01

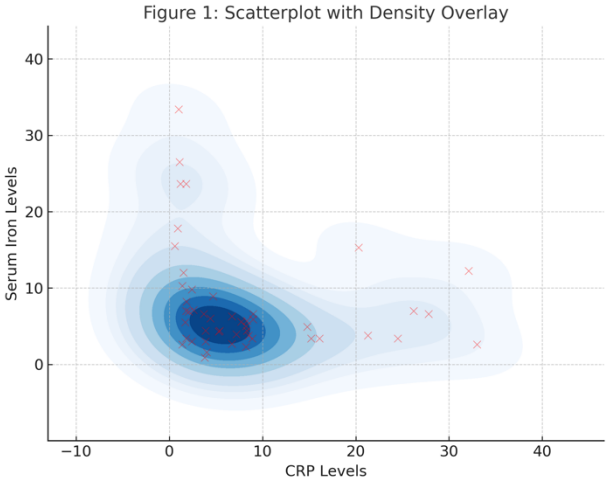

Figure 1: Scatterplot with density overlay illustrating the relationship between CRP levels and serum iron levels. The scatterplot highlights individual data points, while the density overlay visualizes areas of higher data concentration. This figure emphasizes the inverse correlation between CRP and serum iron levels, suggesting the impact of inflammation on iron metabolism.

Subgroup analysis revealed that patients with a serum CRP concentration exceeding 10 mg/L had an average serum iron concentration of 14.2 µmol/L, significantly lower than the 21.5 µmol/L observed in patients with lower CRP levels (average difference: 7.3 µmol/L, $p < 0.01$). There were no statistically significant differences in serum iron concentrations between genders within the subgroups.

Analyses of MLR models, creative analysis also assert these hypotheses specifying that among the factors associated with serum iron levels, CRP was determined to be of major importance (Beta = -0.12, $p < 0.01$) regardless of the age and sex of persons. Inflammation and MCV were found to be related to serum iron levels as well (Beta = 0.18, $p < 0.01$).

Additional analysis of MLR models revealed that CRP was negatively correlated with transferrin saturation (TSAT) and positively correlated with serum ferritin ($r = 0.35$, $p < 0.05$), which is also in line with ferritin's behaviour in inflammation. Positive relationship was also noted between elevated CRP and erythrocyte RDW ($r = 0.22$, $p < 0.05$) that occurs in inflammation due to variation in erythrocyte size.

Figures 1–3 visually support these conclusions. Figure 1 illustrates the negative correlation between CRP and serum iron. The density overlay plot shows that as CRP levels rise, serum iron concentrations decrease, with scatter points more densely concentrated in this area. Figure 2 makes a comparison of serum iron levels in patients having high CRP and normal ones, underlining the considerable drop in CRP level which correlates with increased vasculature around the liver. In Figure 3, the association of CRP and serum iron levels is investigated in more detail considering gender and age. The heat map illustrates the density distribution while the scatter overlays show trends specific to sex and age.

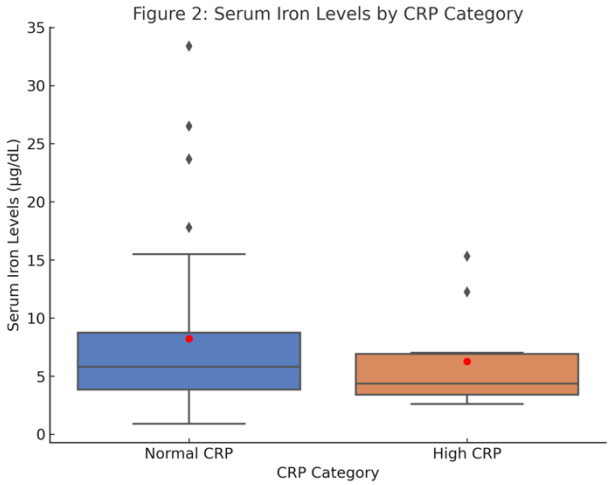

Figure 2: Box plot comparing serum iron levels between patients with high CRP levels and those with normal CRP levels. The plot shows the median, interquartile range, and outliers for each group, with individual data points overlayed. Mean serum iron levels are indicated by red markers. This figure highlights the significant reduction in serum iron levels associated with elevated CRP levels.

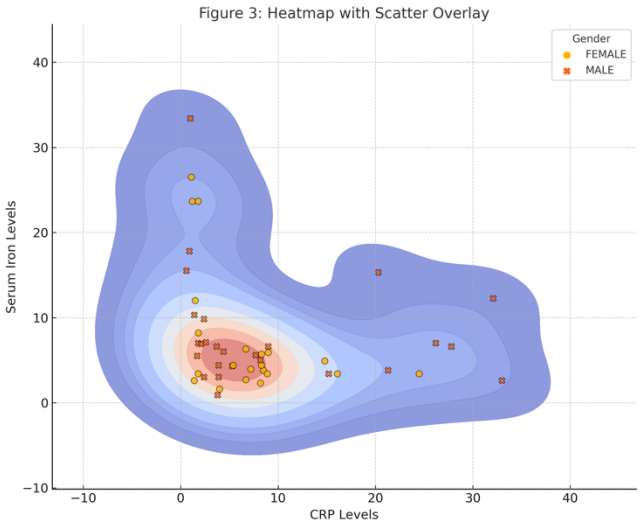

Figure 3: Heatmap with scatter overlay illustrating the relationship between CRP levels and serum iron levels. The heatmap represents the density of data points, while the scatterplot overlays differentiates gender using distinct markers. Age is indicated by the distribution of data points across CRP and serum iron levels. This figure highlights the inverse correlation between CRP and serum iron levels and visualizes demographic trends.

DISCUSSION

The fusion of inflammation and iron metabolism is one of the key components influencing the understanding of systemic responses to chronic diseases. In this context, elevated CRP levels and

reduced serum iron concentrations, as predicted by the model, demonstrate the metabolic and hematological effects of inflammation.[2,14] These findings support the existing literature on the observed phenomena, i.e., the absence of ferryin in the bloodstream is accompanied with elevated levels of inflammatory markers.

In essence, cytokines released during an inflammatory response disrupt hepcidin production, triggering a cascade of related inflammatory processes. Macrophages create mechanisms that inhibit intestinal iron absorption, further reducing iron availability.[3,6] This process disrupts intestinal iron absorption and increases hepcidin production. This mechanism accounts for reduced serum iron levels despite adequate iron stores, a hallmark feature of anemia of chronic disease (ACD).[1,3,6] This pathophysiological model is further supported by the significant inverse relationship between CRP levels and serum iron concentrations.[6,10,13]

The biological implications of the findings are multifaceted. As mentioned earlier, the strong link between the concentration of CRP and the serum iron levels serves as a clinical diagnostic marker of any inflammatory diseases and their assorted anemia.[6,12,13,15] Also, iron serum levels show that women had lower levels than men, indicating some physiological differences by sex with respect to the possible effects of inflammation. There were no gender-based differences in the relationship between CRP and serum iron levels, indicating that the inflammatory response is consistent across genders.[16]

There is also a weak negative correlation between CRP and transferrin saturation, and a positive relationship between CRP and serum ferritin, which, however, reflect the relationship between inflammation and iron transport and storage.[13] Elevated levels of ferritin during an acute phase can mask the presence of iron deficiency, resulting from inflammatory conditions, thus, great care needs to be taken in interpreting iron studies during these states.[8]

There are mentions of certain Saudi populations that have been previously studied and were found to have high rates of anemia, this calls for a research approach that is deeper in nature, so that it can take into consideration the region and the people who may be affected by iron metabolism.[9] Some of the peculiar traits of these groups are genetic polymorphisms as well as dietary customs and co-morbidities that can influence response to inflammation and its consequences on various hematological parameters.[10,17]

The results contribute to understanding inflammation and its impact on alterations in hematological parameters. It was evident that modification in serum iron levels is likely to have a direct influence on the size of red blood cells that correlate to the mean corpuscular volume, which is paramount in the diagnosis and treatment of anemias.[18,19] The various inverse ratios that exist between the content of hemoglobin and the counting of red cells indicate the degree of iron deficiency and the resulting compensatory hematopoietic effect.[20,21]

Future studies should investigate the role of hepcidin and cytokines in influencing CRP reactivity through iron depletion mechanisms. Also, further studies of a longitudinal nature even in the context of inflammation and iron parameters being studied in greater detail would result in a better understanding of the pathological progression of anemia with chronic disease. Targeted interventions addressing the pathways of hepcidin and cytokines may help mitigate these pathological disruptions.

CONCLUSION

The simultaneous measurement of elevated CRP and reduced serum iron levels highlights a significant relationship between inflammation and iron metabolism in the studied cohort. The significant drop in the serum iron levels due to a high CRP level provides strong evidence for the inflammatory processes to play an active role in the anemia of chronic disease. These findings highlight an inflammation biological

process disruption that is often caused by increased hepcidin shuttling iron away from the circulation, leading to alteration in hematologic parameters.

The strong associations that were found between CRP, serum iron, and the rest of the hematologic indices point to an important clinical significance of the use of inflammatory factors with the aim of diagnosing and treating anemia. Moreover, the study depicts the specific population aspects especially in areas where anemia is highly prevalent and therefore there is a need for such interventions.

The links between a state of inflammation and functions of iron metabolism need to be further studied as potential medicinal targets. Understanding these mechanisms can enhance the diagnosis and management of inflammation-associated anemia. The present study opens up new perspectives for studying the bidirectional relationship between systemic inflammation and hematopoietic functions.

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Conflicts of interest

The author declares no conflict of interest relevant to this article.

REFERENCES

1. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood*. 2019;133(1):40-50.
2. Papanikolaou G, Pantopoulos K. Systemic iron homeostasis and erythropoiesis. *IUBMB Life*. 2017;69(6):399-413.
3. Gangat N, Wolanskyj AP. Anemia of chronic disease [published correction appears in Semin Hematol. 2014 Apr;51(2):e1]. *Semin Hematol*. 2013;50(3):232-238.
4. Safiri S, Kolahi AA, Noori M, et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *J Hematol Oncol*. 2021;14(1):185.
5. Aydin Z, Gursu M, Karadag S, et al. The relationship of Prohepcidin levels with anemia and inflammatory markers in non-diabetic uremic patients: a controlled study. *Ren Fail*. 2014;36(8):1253-1257.
6. Pagani A, Nai A, Silvestri L, Camaschella C. Hepcidin and Anemia: A Tight Relationship. *Front Physiol*. 2019;10:1294.
7. Hakami W, Dobie G, Alneami KA, et al. Assessing Nutritional Anemia Among University Students in Jazan, Saudi Arabia: A Public Health Perspective. *J Blood Med*. 2024;15:51-60.
8. Gari M. Prevalence of Iron Deficiency Anemia among Female Elementary School Children in Northern Jeddah, Saudi Arabia. Journal of King Abdulaziz University-Medical Sciences 2008;15(1):63–75.
9. Al Hassan NN. The prevalence of iron deficiency anemia in a Saudi University female students. *J Microsc Ultrastruct*. 2015;3(1):25-28.
10. Alquaiz AM, Gad Mohamed A, Khoja TA, et al. Prevalence of anemia and associated factors in child bearing age women in riyadh, saudi arabia. *J Nutr Metab*. 2013;2013:636585.
11. Chen MX, Kuehne N, Mattman A, Liu J, Van der Gugten G, Wright B. Clinical interpretation of serum hepcidin-25 in inflammation and renal dysfunction. *J Mass Spectrom Adv Clin Lab*. 2022;24:43-49.

12. D'Angelo G. Role of hepcidin in the pathophysiology and diagnosis of anemia. *Blood Res*. 2013;48(1):10-15.
13. Ross SL, Tran L, Winters A, et al. Molecular mechanism of hepcidin-mediated ferroportin internalization requires ferroportin lysines, not tyrosines or JAK-STAT. *Cell Metab*. 2012;15(6):905-917.
14. Ganz T. Systemic iron homeostasis. *Physiol Rev*. 2013;93(4):1721-1741.
15. Galesloot TE, Vermeulen SH, Geurts-Moespot AJ, et al. Serum hepcidin: reference ranges and biochemical correlates in the general population. *Blood*. 2011;117(25):e218-e225.
16. Mantadakis E, Panagopoulou P, Kontekaki E, Bezirgiannidou Z, Martinis G. Iron Deficiency and Blood Donation: Links, Risks and Management. *J Blood Med*. 2022;13:775-786.
17. Haraguchi K, Uto H, Ohnou N, et al. Serum prohepcidin levels are potential prognostic markers in patients with multiple myeloma. *Exp Ther Med*. 2012;4(4):581-588.
18. Breymann C. Iron Deficiency Anemia in Pregnancy. *Semin Hematol*. 2015;52(4):339-347.
19. Smith GA, Fisher SA, Doree C, Di Angelantonio E, Roberts DJ. Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors. *Cochrane Database Syst Rev*. 2014;2014(7):CD009532.
20. Owaidah T, Al-Numair N, Al-Suliman A, et al. Iron Deficiency and Iron Deficiency Anemia Are Common Epidemiological Conditions in Saudi Arabia: Report of the National Epidemiological Survey. *Anemia*. 2020;2020:6642568.
21. Pasricha SR, McQuilten Z, Westerman M, et al. Serum hepcidin as a diagnostic test of iron deficiency in premenopausal female blood donors. *Haematologica*. 2011;96(8):1099-1105.