DOI: https://doi.org/10.53350/pjmhs2023174427

ORIGINAL ARTICLE

Association of Serum Ferritin with C Reactive Protein in Iron Deficiency Anaemia

KIRAN AAMIR[1], SIDRAH[2], SAFIAN AHMED[3], HAJI MUHAMMAD AFTAB ALAM[4], DURGA DEVI[5], AQSA JUNEJO[6], AAMIR RAMZAN[7], FARHAN AHMED SHAIKH[8]

[1]*Associate professor Pathology Department, Liaquat university of Medical and health sciences jamshoro Hyderabad.*
[2]*Resident Histopathology , Lecturer at Bilawal Medical College for boys , Liaquat university of Medical and health sciences jamshoro Hyderabad.*
[3]*Senior Registrar in Medicine Department, Isra University Hyderabad*
[4]*Consultant Medical Specialist, Combined Military Hospital Giligit Pakistan*
[5]*Lecturer in Pathology Department Bilawal medical college for boys, Liaquat university of Medical and health sciences jamshoro Hyderabad*
[6]*Demonstrator in Pathology Department, Bilawal Medical College for boys, Liaquat university of Medical and health sciences jamshoro Hyderabad*
[7]*Lecturer in pathology Department Liaquat university of Medical and health sciences jamshoro Hyderabad*
[8]*Lecturer, Consultant Haematologist, Pathology Department, Bilawal Medical College for boys,Liaquat university of medical and health sciences jamshoro Hyderabad*
Corresponding author: Kiran Aamir, Email: drkiran73@yahoo.com, Cell: 03342823704

ABSTRACT

Objective: The purpose of this study was to determine whether or not individuals with iron deficiency anemia and an underlying inflammatory condition had a connection between serum ferritin as an acute phase reactant and C - reactive protein.
Study Design: Cross-sectional/Prospective study
Place and Duration: Liaquat university of Medical and health sciences jamshoro Hyderabad. January 2022 to December 2022
Methods: This research comprised 136 individuals who were suffering from iron deficiency anemia. After getting informed written consent detailed demographics of enrolled cases were recorded. Using an automated hematology analyzer (Mindray BC-5000), the parameters of the blood were analyzed. Serum ferritin levels were used to classify each patient into one of three categories. Serum ferritin levels were divided into three groups: Group I (serum ferritin <10 µg/L), Group II (11–150 µg/L), and Group III (>150 µg/L).SPSS version 23.0 was used to analyze the data. Statistical analysis was conducted using Pearson's correlation tests.
Results: In current study patients mean age was 31.13±6.75 years and had mean BMI 24.6±3.52 kg/m^2. There were majority 74 (54.4%) males and 62 (45.6%) females in this study. Majority of the patients 81 (59.6%) were had low ferritin <10 µg/L, followed by normal ferritin 11–150 µg/L in 45 (33.1%) cases and 10 (7.4%) cases had high ferritin >150 µg/L. We found strong co-relation of C reactive protein and high level of serum ferritin with p value <0.002. Serum ferritin levels were negatively correlated with hemoglobin.
Conclusion: We concluded in this study that levels of serum ferritin was positively associated with C-reactive protein (CRP). In patients with underlying deficiency of iron, secondary inflammation may increase the level of ferritin in serum.
Keywords: Ferritin, Haemoglobin, Iron Deficiency Anaemia, C-Reactive Protein

INTRODUCTION

The most frequent cause of anaemia in the world, iron deficiency, is mostly a result of nutritional deficits, particularly in sub-Saharan Africa [1]. When a patient has a chronic inflammatory condition such chronic kidney disease (CKD), inflammatory bowel disease (IBD), or chronic heart failure (CHF), functional iron shortage can also develop as a result of iron sequestration in the reticuloendothelial system [2].

A low blood haemoglobin (Hb) level must be shown in the presence of depleted iron stores in order to diagnose iron deficiency anaemia (IDA) [3]. Since serum ferritin is an acute phase reactant, its usefulness in inflammatory states is limited. Serum ferritin is the most sensitive non-invasive biomarker of iron storage [3]. The World Health Organization's (WHO) suggested cut-off of less than 15 g/L for serum ferritin, which is used to identify iron insufficiency in adults, can be compromised by the presence of inflammation. WHO had previously advised a cut-off of 30 g/L in environments with elevated inflammation, however this has recently been changed to 70 g/L [3,4]. When diagnosing iron insufficiency in people with CKD or IBD, several recommendations have suggested a cut-off of 100 g/L [5,6].

There are limitations built into other iron status biomarkers. For instance, serum iron levels vary throughout the day, peaking in the morning, and have been demonstrated to decrease with an increase in body mass index (BMI) [7,8]. The measurement of blood iron and transferrin levels is necessary for the computation of serum transferrin saturation (TSat), which means that factors affecting these two analytes can have an impact on the result. TSat is a helpful marker, particularly for detecting iron overload. In individuals with chronic inflammatory conditions, TSat has been suggested as a useful test for determining iron insufficiency, with a TSat < 20% indicating iron shortage [2]. A test called the soluble transferrin receptor can tell the difference between iron deficiency anaemia and secondary chronic illness anaemia, where the soluble transferrin receptor is typically elevated in the former. The test, however, is not easily accessible in sub-Saharan Africa and can be impacted by illnesses related to erythroid hyperplasia.

There have been several methods put out to address the bias in ferritin measurement brought on by inflammation[9], but there hasn't been agreement on how to employ APPs to account for the impact of inflammation on ferritin concentration. C-reactive protein (CRP) and -1 acid glycoprotein (AGP) are the most often employed inflammatory indicators in nutritional research and clinical practise.[10] Failure to consider acute-phase proteins could have a significant impact on assessments of micronutrient deficiency prevalence, particularly those relating to iron deficiency, in communities with high inflammation prevalence.[10]

Since there are no case records of malaria or schistosomiasis infections in Cuba and the country has access to clean water and sanitary facilities, it is believed that the population there has low levels of inflammation[10]. Although there are additional risk or morbidity variables in Cuba related with inflammation, such as obesity, asthma, acute diarrheal disorders (ADD), acute respiratory infections (ARI), and other illnesses, it is vital to examine inflammation when analysing the population's iron status.[11]

Since 1987, the National Institute of Hygiene, Epidemiology, and Microbiology (INHEM) of Cuba has been in charge of planning, implementing, and monitoring various prevention and control programmes for iron status. In 2008, the Council of Ministers created the Comprehensive Plan for Prevention and Control of Iron-deficiency Anaemia.[11] Programme surveillance is also part of it, along with programmes for diverse diets, fortified foods, and food supplements. The frequency of iron deficiency anaemia among preschoolers is still high in spite of this.

The prevalence of metabolic syndrome, a known source of persistent low-grade inflammation, has increased in sub-Saharan Africa as a result of urbanisation [9]. Iron deficiency in persons with chronic inflammation is still difficult to accurately detect. The release of the iron regulating hormone hepcidin, which causes iron to be stored in the reticulo-endothelial system, is one way that inflammatory cytokines like interleukin 6 regulate iron metabolism [10]. In order to diagnose iron deficiency, particularly in populations with inflammation, there is no agreement on the optimum way to use iron status markers such ferritin and TSat [11]. Concerns concerning the applicability of published cut-offs in determining iron deficiency in an African population are further raised by the dearth of published data from sub-Saharan Africa (SSA) on reference intervals for markers of iron status. Since patients in SSA may have inflammation from both infectious and non-communicable diseases, it is important to assess the diagnostic accuracy of tests like ferritin in identifying probable iron deficient anaemia. In these circumstances, the amount of soluble transferrin (sTfR) or hepcidin can be used to measure the status of the body's iron levels without causing harm to the patient.

A lack of vitamin B, thyroid disease, renal disease, or liver disease are just a few of the conditions that might cause a person's haematocrit or mean corpuscular volume (MCV) to drop. Anaemia causes these conditions to occur, though. The Centres for Disease Control and Prevention (CDC) and World Health Organisation (WHO) jointly recommended the utility of one or two acute phase reactants, e.g. C-reactive protein, for correction of ferritin when an inflammatory condition is evident because it was obvious that certain investigations of acute phase reactions were required for interpretation of ferritin concentration to assess the status of body iron. (9) In order to assess the relationship between ferritin and C-reactive protein in patients with iron deficient anaemia and normal or elevated ferritin levels as a result of concomitant inflammatory status, this study was done.

MATERIAL AND METHODS

This Cross-sectional/Prospective study was conducted at Liaquat university of Medical and health sciences jamshoro Hyderabad and comprised of 136 patients. In this study, participants ranged in age from 12 to 55 years, and all of them suffered from hypochromic microcytic anaemia. Iron overload syndrome patients and those who were already receiving iron replacement therapy were not included in the study. Patients who had other medical problems, such as drinking, pregnancy, bleeding disorders, or hemoglobinopathies, were also not allowed to participate.

Five millilitres (5 mL) of venous whole blood were drawn after obtaining informed consent; 3 mL was transferred to tubes containing gel for evaluation of serum ferritin and C-Reactive protein, and 2 mL was transferred to an EDTA-containing tube for a full blood count. The automated haematology analyzer Mindray BC-5000 was used to check the blood's properties. Mindray CL1000i electrochemiluminesence assay was utilised to evaluate serum ferritin levels. The immunoturbidimetric determination of C-reactive protein was performed with a Mindray BS-240 automated chemistry analyzer. Patients were stratified into three groups based on their ferritin levels: Group I included those with a low ferritin level (11 g/L), Group II included those with a normal ferritin level (11-150 g/L), and Group III included those with a high ferritin level (>150 g/L). SPSS 23.0 was used for all statistical analysis. The link between iron deficient anaemia and serum ferritin and C-reactive protein levels was determined using Pearson's correlation test. Statistical significance is denoted by the P-value.

RESULTS

In current study patients mean age was 31.13±6.75 years and had mean BMI 24.6±3.52 kg/m^2. There were majority 74 (54.4%) males and 62 (45.6%) females in this study. Mean hemoglobin was 9.1±6.16 g/dl, mean HCT was 29.4±3.11 ug/L, mean MCV was 64.8±7.26 fl, MCH was 21.4±5.13 Pl and MCHC was 30.3±5.37 g/dl.(table 1)

Table-1: Demographics data of the enrolled cases

Variables	Frequency (n=136)	Percentage
Mean age (years)	31.13±6.75	
Mean BMI (kg/m^2)	24.6±3.52	
Gender		
Male	74	54.4
Female	62	45.6
Mean hemoglobin (g/dl)	9.1±6.16	
Mean HCT (ug/L)	9.1±6.16	
Mean MCV (fl)	64.8±7.26	
Mean MCH (Pl)	21.4±5.13	
Mean MCHC (g/dl)	30.3±5.37	

Majority of the patients 81 (59.6%) were had low ferritin <10 µg/L, followed by normal ferritin 11–150 µg/L in 45 (33.1%) cases and 10 (7.4%) cases had high ferritin >150 µg/L.(figure-1)

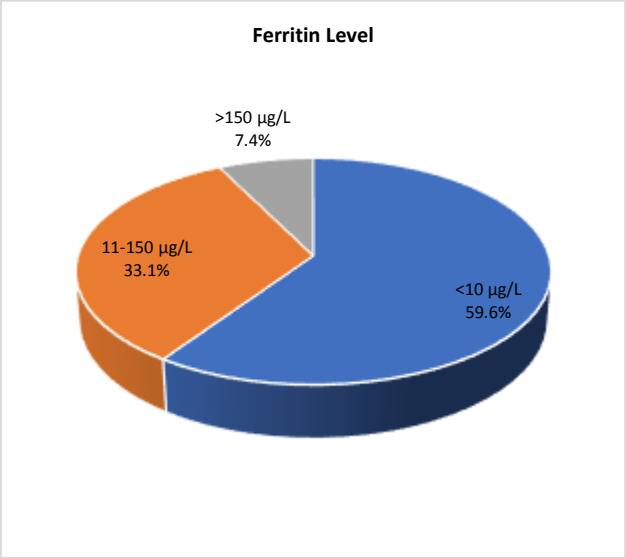

Figure-1: Association of ferritin levels among all cases

We found strong co-relation of C reactive protein and high level of serum ferritin with p value <0.002.(table 2)

Table-2: Association of C-reactive protein with ferritin levels

Variables	Group I <10 µg/L	Group II 11-150 µg/L	Group II >150 µg/L
Mean CRP (mg/L)	6.3±3.44	24.13±2.25	35.13 ± 3.38

Serum ferritin levels were negatively correlated with hemoglobin.(table 3)

Table-3: Correlation Analysis Using the Pearson Method for Anaemia Due to Iron Deficiency

Variables	Pearsons Value
Haemoglobin	-0.55
C-Reactive Protein	0.88
Ferritin	0.71

DISCUSSION

Anaemia due to a lack of iron is a major public health issue worldwide. Serum ferritin is used as an indicator of iron status in a variety of healthcare settings.[16] It is not always possible to tell if a patient has iron deficiency anaemia simply by looking at their ferritin levels, which can be high or normal if there is an underlying inflammatory, chronic illness, or infection. Approximately 54.4 percent of the participants in this survey were male, whereas just

45.6 percent were female. Khan et al. also got pretty much the same results.[17]In cases of inflammation, UNICEF and WHO advise using a C-reactive protein (CRP) or other inflammatory marker to evaluate iron levels.[18]

The biomarkers indicating the inflammatory and Nutrition Determinants of Anaemic patients (BRINDA) have shed light on the measurement of inflammatory indicators while assessing iron status at the population level. The importance of measuring biochemical markers of subclinical inflammation has been suggested by recent studies in children that show how indicators of inflammation or infection change depending on sociodemographic factors, environmental factors, and morbidity information alone cannot reliably detect or assess the infection or inflammation.[19] The acute phase reactant (APR) has several phases, ranging from acute inflammation (e.g., quick start within 1 h) to chronic infection (e.g., rising after 24 h and lasting 4- 5 days). Concentrations of CRP may be significant because they demonstrate these different APR phases.[20]

As a result of underlying inflammatory conditions, group II and group III, which had normal and high ferritin levels, respectively, displayed higher levels of CRP and indicated a positive association between CRP and ferritin in our data. It also demonstrated that, from low to high ferritin levels, haemoglobin levels decreased while ferritin and CRP levels rose, which was consistent with findings by Khan et al. [18] In addition, Kalantar et al. found that patients receiving haemodialysis also had high ferritin levels as a result of MICS.[21]

Patients with diabetes mellitus type 2 were studied by Allam et al. using high levels of ferritin and hsCRP as markers of inflammation. [22]There is a favourable link between high ferritin levels and the risk of obesity and metabolic syndrome, according to a study of nutritional health and examination survey by Gillum et al. [23] Similar findings were revealed by our research.

Due to these findings, the application of ferritin as a new diagnostic for iron deficient anaemia diagnosis in inflammatory underlying diseases seems debatable. [24,25] In our investigation, ferritin was not shown to be the best marker for evaluating body iron in inflammatory situations at the root. Despite the fact that there is a positive link between ferritin and inflammation, adding C-reactive protein has been proved to be helpful in determining the body's iron status and in aiding in the early detection and treatment of patients who are iron deficient. However, it is advised to conduct studies on bigger populations in order to evaluate different aspects and obtain substantial correlations.

The most accurate indicator of iron insufficiency is a decrease in plasma ferritin levels. When there is inflammation, ferritin concentration rises. The state of the body's iron is assessed using CRP. [26] Children with inflammatory disorders had greater serum ferritin levels than children without inflammation in our study. Iron regulating hormone, or hepcidin, in fact inhibits the circulation of iron under inflammatory conditions. Thus, endogenous iron rather than dietary iron is utilised in erythropoiesis.[27] Serum ferritin levels rise as a result of this. Knowles et al. came to a similar conclusion, finding that children with inflammation had higher serum ferritin concentrations than children without inflammation.[28]

CONCLUSION

We concluded in this study that levels of serum ferritin was positively associated with C-reactive protein (CRP). In patients with underlying deficiency of iron, secondary inflammation may increase the level of ferritin in serum

REFERENCES

1 Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013; 1(1):e16–25. https://doi.org/10.1016/S2214-109X(13)70001- 9 PMID: 25103581

2 Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol. 2017; 92(10):1068–78. https://doi.org/10.1002/ajh.24820 PMID: 28612425

3 WHO. Serum ferritin concentrations for the assessment of iron status in individuals and populations: technical brief. Geneva: World Health Organization; 2020.

4 WHO. Serum ferritin concentrations for assessment of iron status and iron deficiency in populations. 2011.

5 Dignass AU, Gasche C, Bettenworth D, Birgegard G, Danese S, Gisbert JP, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015; 9(3):211–22. https://doi.org/10.1093/ecco-jcc/jju009 PMID: 25518052

6 Locatelli F, Barany P, Covic A, De Francisco A, Del Vecchio L, Goldsmith D, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant. 2013; 28(6):1346–59. https:// doi.org/10.1093/ndt/gft033 PMID: 23585588

7 Kim J-W, Kim DH, Roh YK, Ju SY, Nam H-Y, Nam G-E, et al. Serum Ferritin Levels Are Positively Associated With Metabolically Obese Normal Weight: A Nationwide Population-Based Study. Medicine. 2015; 94(52):e2335–e. https://doi.org/10.1097/MD.0000000000002335 PMID: 26717370

8 Khan A, Khan WM, Ayub M, Humayun M, Haroon M. Ferritin Is a Marker of Inflammation rather than Iron Deficiency in Overweight and Obese People. Journal of Obesity. 2016; 2016:1–7.

9 World Health Organization. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Vitamin and Mineral Nutrition Information System (WHO/NMH/NHD/MNM/11.2) [Internet]. Geneva: World Health Organization; 2011 [cited 2014 Jul 5]. 5 p. http://www.who.int/vmnis/indicators/serum_ferritin.pdf

10 Raiten DJ, Ashour FAS, Ross AC, Meydani SN, Dawson HD, Stephensen CB, et al. Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence (INSPIRE). J Nutr. 2015 May;145(5):1039S–108S.

11 Petri N, Olofin I, Hurrell RF, Boy E, Wirth JP, Moursi M, et al. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: a systematic analysis of national surveys. Nutrients [Internet]. 2016 Nov 2 [cited 2020 Mar 10];8:693. Available at. Available at: https://doi.org/10.3390/nu8110693

12 Omuse G, Maina D, Hoffman M, Mwangi J, Wambua C, Kagotho E, et al. Metabolic syndrome and its predictors in an urban population in Kenya: A cross sectional study. BMC Endocrine Disorders. 2017;17(1)

13 Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. Annu Rev Nutr. 2006;26:323–42. doi: 10.1146/annurev.nutr.26.061505.111303

14 Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr. 2015;102(6):1585–94. doi: 10.3945/ajcn.114.103366

15 Omuse G, Ichihara K, Maina D, Hoffman M, Kagotho E, Kanyua A, et al. Determination of reference intervals for common chemistry and immunoassay tests for Kenyan adults based on an internationally harmonized protocol and up-to-date statistical methods. PLoS One. 2020;15(7):e0235234. doi: 10.1371/journal.pone.0235234

16 Kalantar K. Association of serum ferritin and measures of inflammation, Nutrition and iron in Hemodialysis patients. JNDT. 2004; 19(1): 141-51.

17 Khan A, Khan WM, Ayub M, Humayun M, Haroon M. Ferritin is a marker of inflammation rather than iron deficiency in over weight and obese. J Obes; 2016.: 1937320).

18 WHO/UNICEF, UNU. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. Geneva, World Health Organization, 2001. [id 10.1371/jounal. pone.015505].

19 Namaste SM, Rohner F, Huang J, Bushan NL, Flores-Ayala R. Adjusting ferritin concentrations for inflamma-tion: Biomarkers reflecting inflammation and nutritional deter-minants of anemia (BRINDA) project. Am J Clin Nutr 2017; 106(l): 359S–371S.

20 Gupta Bansal P, Singh Toteja G, Bhatia N, Kishore Vikram N, Siddhu A, Kumar Garg A, et al. Deficiencies of serum ferritin and vitamin B12, but not folate, are common in adolescent girls residing in a slum in Delhi. Int J Vit Nutr Res 2015; 85(1-2): 14–22.

21 Alam F, Fatima F, Orakzai S, Iqbal NT, Fatima SS. Elevated levels of ferritin and hs-CRP in type 2 diabetes. J Pak Med Assoc. 2014; 64(12):1389–91.
22 Gillum RF. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men the third national health and nutrition examination survey, Int J Obesity. 2001; 25(5): 639–45.
23 Eftekhari MH, Mozaffari-Khosravi H, Shidfar F. The relationship between BMI and iron status in iron-deficient adolescent Iranian girls. Public Health Nutr. 2009 12(12): 2377–81.
24 Huang YF1, Tok TS2, Lu CL3, Ko HC4, Chen MY5, Chen SC6. Relationship between overweight and iron deficiency in adolescents. Pediatr Neonatol. 2015; 56(6): 386–92.
25 O'Brien HT, Blanchet R, Gagn´e D, Lauzi`ere J, V´ezina C. Using soluble transferrin receptor and taking inflammation into account when defining serum ferritin cutoffs improved the diagnosis of iron deficiency in a group of Canadian preschool Inuit children from Nunavik. Anemia. 2016: 643021.
26 Kim JW, Kim DH, Roh YK. Serum ferritin levels are positively associated with metabolically obese normal weight: a nationwide population-based study. Medicine 2015; 94(52): e2335.
27 Huang YF, Tok TS, Lu CL, Ko HC, Chen MY, Chen SC. Relationship between overweight and iron deficiency in adolescents. Pediatr Neonatol 2015; 56(6): 386–392
28 Huang YF, Tok TS, Lu CL, Ko HC, Chen MY, Chen SC. Relationship between overweight and iron deficiency in adolescents. Pediatr Neonatol 2015; 56(6): 386–392