IRON DEFICIENCY WITH AND WITHOUT ANEMIA IN PATIENTS OF HEART FAILURE WITH REDUCED EJECTION FRACTION

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ABSTRACT

Iron deficiency (ID) is the most common dietary deficiency in the world and the leading cause of anemia. Iron deficiency can lead to symptoms both due to the lack of iron and due to the resultant anemia. Heart failure patients can develop iron deficiency (ID) by various mechanisms. Considering that iron levels may vary in different geographical regions according to economic, environmental, infectious, and genetic factors, this study was particularly devoted for studying iron deficiency in heart failure patients irrespective of presence of anemia. Patients >18 years diagnosed with heart failure on the basis of clinical and biochemical parameters and an ejection fraction ≤40% on transthoracic echocardiography were recruited and biochemical parameters and iron profile was analysed for the presence of iron deficiency. The study subjects' mean ejection fraction was 35.02±4.56%. The mean age was 59.33± 14.06 years. The study involved 90 patients, of whom 69 (76.7%) were classified as iron deficient because their S. ferritin levels were less than 100 µg/L and/or their transferrin saturation was less than 20%. The remaining 21 patients were classified as having normal iron levels. NT pro-BNP was significantly higher in iron deficient cases than those with normal iron (7822±7047 vs. 2673±1806 pg/ml). In the present study 76.7% of individuals with heart failure and a decreased ejection fraction had iron insufficiency. Further studies with larger sample size to correlate grades of HF with ID strata are recommended. This has got therapeutic potential and lays scaffold for prospective studies.

KEYWORDS: Iron Deficiency, Anemia, Heart failure with reduced Ejection fraction.

INTRODUCTION

Many biological functions of the body require iron, a few of them are synthesis of hemoglobin, myoglobin, as a cofactor or catalyst in various biochemical reactions, cell proliferation and regulation, synthesis of DNA, and mitochondrial electron transport (1). The body stores most of its iron in the liver and bone marrow with the remainder being found in the circulating red blood cells that make up hemoglobin (2). Iron is one among the enzymes, along with myoglobin, that are engaged in various physiological activities. Approximately 2 billion individuals worldwide suffer from the most prevalent dietary deficiency and the primary cause of anemia is iron deficiency (ID) (3) For men, the normal range for serum iron levels is 75–150 mcg/dL (13–27 micromol/L) and women's levels are 60–140 mcg/dL (11–25 micromol/L). Transferrin saturation (T-sat) should range from 20 to 50%, and total iron-binding capacity (TIBC) should be between 250 and 450 mcg/dL (45 to 81 micromol/L). Serum iron levels are elevated in iron-overload syndromes and hemolytic disorders and decreased in absolute iron deficiency conditions and other chronic diseases. Iron-binding capacity increases and transferrin saturation decreases in the presence of iron deficiency. There is a correlation between serum ferritin levels and total body iron stores. Iron deficiency can lead to symptoms both due to the lack of iron and also consequent to anemia. Iron deficiency is common in heart failure patients for a variety of reasons, including the co-occurrence of comorbidities such as chronic kidney disease, low iron intake (resulting from anorexia and low-protein diets), gastrointestinal blood loss (induced by coagulation abnormalities or platelet dysfunction; caused by uremia, anticoagulants, or antiplatelet agents), and iron malabsorption (resulting from either uremia-related intestinal cell dysfunction or congestive cardiac failure), or as a result of medications like proton pump inhibitors and phosphate binder resin which also bind iron).

Heart failure itself may give rise to iron deficiency (ID) through various mechanisms. One theory of ID in heart failure is proposed to be caused by a rise in

hepcidin, an iron-regulating protein, This stops the reticuloendothelial system and enterocytes from releasing iron. In the context of systemic inflammation, hepcidin levels may be elevated (4). Other factors such as reduced gastric emptying, When heart failure worsens, there may be more substantial effects from decreased iron-rich food intake when coexisting anorexia, intestinal dysfunction with mucosal oedema, increased blood loss from anticoagulants, and gastric ulcers (5). According to heart failure guidelines published by the European Society of Cardiology, tests for iron deficiency, serum ferritin, and transferrin saturations should be performed on all patients diagnosed with heart failure (6). Considering that iron levels may vary in different geographical regions according to economic, environmental, infectious, and genetic factors, this study was particularly devoted for estimation Iron deficiency is prevalent among tertiary care patients with heart failure centre in north Indian region.

METHODOLOGY

For this study, all consecutive patients of heart failure attending medicine and cardiology indoors and opds of Era's Lucknow Medical College & Hospital were considered. The following inclusion and exclusion criteria bound the study's sample frame. Patients aged >18 years diagnosed with heart failure on the basis of clinical and biochemical parameters with Ejection fraction ≤ 40% on echocardiography were included. Patients who had taken iron orally or intravenously within the previous three months were not included. The Institutional Ethics Committee granted ethical approval, and each subject gave informed consent prior to the study. Demographic details and clinical findings of the 90 patients with HFrEF, or decreased ejection fraction, heart failure were recorded along with laboratory findings. The data was analyzed using appropriate statistical tests.

RESULTS

This study found the prevalence of iron deficiency among coronary artery disease patients who had an EF of less than 40% at Era's Lucknow Medical College & Hospital's department of medicine and cardiology. A total of 90 patients of HfrEF were enrolled . Ejection fraction of patients ranged between 24-40% and mean EF was 35.02±4.56%. Age of heart failure patients ranged between 22 & 85 years, and the average age was 59.33±14.06 years. The study included 90 patients, and their iron profiles were as follows: 76.7 percent of the 69 individuals exhibited 100 g/L of S. ferritin or a 20% transferrin saturation level. These patients were found to be iron deficient. Figure 1 and Table 1. The remaining 21 patients had S. ferritin levels greater than 100 g/L and transferrin saturation greater than 20%, putting them in the normal or sufficient iron category. There was a significant age difference between individuals with normal iron levels and those with iron deficiency (53.7117.09 vs. 61.0412.65 years). Among the study subjects; 33 (36.7%) were females and rest 57 (63.3%) were males. Proportion of females was slightly higher among iron deficient as compared to those with normal iron levels (37.7% vs. 33.3%) but this difference was not significant statistically. Majority of overall (n=69; 76.7%) as well as iron deficient (75.4%) and normal iron (81.0%) patients were non-vegetarian. Difference in dietary habit of patients in the iron deficient and normal iron groups was not found to be significant. NT pro-BNP which is a biochemical marker of heart failure was found to be substantially higher in iron deficiency compared to the patients' normal iron group (7822±7047 vs. 2673±1806 pg/ml) implicating severity of disease in the iron deficient group. It was shown that individuals with iron deficiency had far lower hemoglobin levels than those with normal iron. (10.99±2.46 vs. 12.32±1.89 g/dl). TLC counts and components of differential count (Neutrophils, lymphocytes, Monocytes and Eosinophils) did not show any significant association with iron deficiency (Table 2).

Sr. no.	Iron parameters	Iron Def. (n=71)	Normal Iron (n=19)	Student 't' test	
		Mean +SD	Mean +SD	't'	'p'
1	Serum Iron	36.68+17.40	86.14+48.96	-7.111	<0.001
2	Serum Ferritin	162.40+192.06	446.29+325.91	-5.017	<0.001
3	TIBC	305.46+92.38	269.57+74.59	1.625	0.108
4	Transferrin saturation	12.33+5.55	31.76+12.83	-9.965	<0.001

Table1 : Observed Iron Profile in two groups of HFrEF patients

Sr. no.	Laboratory parameters	Iron Def. (n=69)		Normal Iron (n=21)		Student 't' test	
		Mn	SD	Mn	SD	't'	'p'
1	NT pro-BNP	7822	7047	2673	1806	3.303	0.001
2	Hemoglobin	10.99	2.46	12.32	1.89	-2.278	0.025
3	TLC	8562	3008	9410	3059	-1.126	0.263
4	Neutrophils	75.00	11.36	78.86	10.55	-1.384	0.170
5	Lymphocytes	20.04	10.73	16.67	8.25	1.326	0.188
6	Monocytes	2.45	1.56	2.33	2.15	0.272	0.786
7	Eosinophils	2.44	2.23	2.14	1.24	0.572	0.569

Table 2: Association of Iron Deficiency with Laboratory parameters

DISCUSSION

Nutritional deficiencies are a well known cause of health disorders. Iron is one of the most important minerals in the human beings. Being an essential component of the fluid tissue, i.e., iron in form of ferritin plays an important role in oxidative phosphorylation by aiding in electron-transfer and oxygen activation (7) . In the heart, the role of iron is not only limited to oxidative phosphorylation process but in its various forms it also has a significant impact on redox signalling by production of reactive oxygen species (ROS) (8). Apart from having these direct roles in various cardiac functions, iron indirectly also affects them owing to its strong relationship with ID. In the setting of anemia exercise capacity of the cardiomyocytes is reduced and there is limited oxygen availability that is essential to carry out oxidative phosphorylation within these specialised cells (9).

Research has demonstrated a link between iron deficiency and heart diseases like heart failure (HF) and coronary artery disease and pulmonary hypertension (6). It not only acts as a risk factor for development of these disorders but also has a detrimental effect on the outcome too. Iron deficiency is an important yet relatively less explored dimension of cardiovascular diseases warranting exploration with respect to its prevalence and impact on disease severity and other outcomes. Therefore, the current study was conducted in HfrEF patients in a tertiary care facility to determine the prevalence of iron deficiency. In current study where more than three-quarters of the HF patients were iron deficient; Jankowska et al (10) found iron deficiency in 37% of their HF patients, probably owing to a higher male dominance (88%) and relatively lower mean age (55 years) as compared to the present study (Mean age 59.33 years; 63.3% males). However, a number of other studies report high prevalence of ID as observed in our study. A number of studies report it to be prevalent in more than two-third HF patients (11). The findings of the present study is comparable to a study from neighbouring state Rajasthan that reported the prevalence of ID to be 76% in HF patients(12). In another study by Arora et al. from India, iron deficiency in HF patients was reported to be 53.8%, thus showing that majority of patients were affected by iron deficiency (13). We failed to derive a significant association of iron deficiency with nutritional status, and hemodynamic parameters of the heart failure patients (Figure 2) in the current study. Compared to the present study, von Haehling et al. in their study enlisted low body weight as a significant risk factor associated with ID (14). The problem of ID in HF patients should not be viewed in traditional context of association of iron deficiency anemia with undernutrition. Even if in nutritional context, it should be viewed in context of malnutrition rather than undernutrition and here the malnutrition implies overweight and obese status which is a known cardiovascular risk factor and is also a predictor of iron deficiency. As far as association of higher NT pro-BNP with ID is concerned, it is reflective of association of physiological manifestation of severity of heart failure with ID. Similar to the present study, Schou et al. found a significant association of NYHA classes of heart failure with ID, thus showing the impact of ID on severity of HF (15). The present study's intriguing results may have a big influence on how patients with coronary artery disease are treated, particularly if their EF is reduced. The role of iron deficiency in HF patients needs to be explored from the view point of prognostic and therapeutic potential.

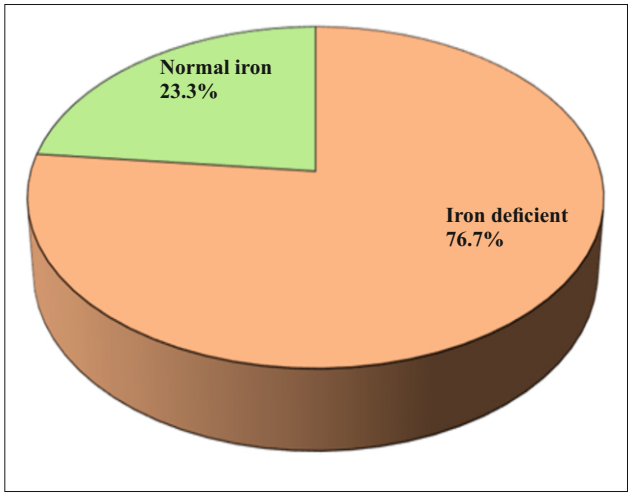

Fig. 1: Distribution of Study population according to Iron Status

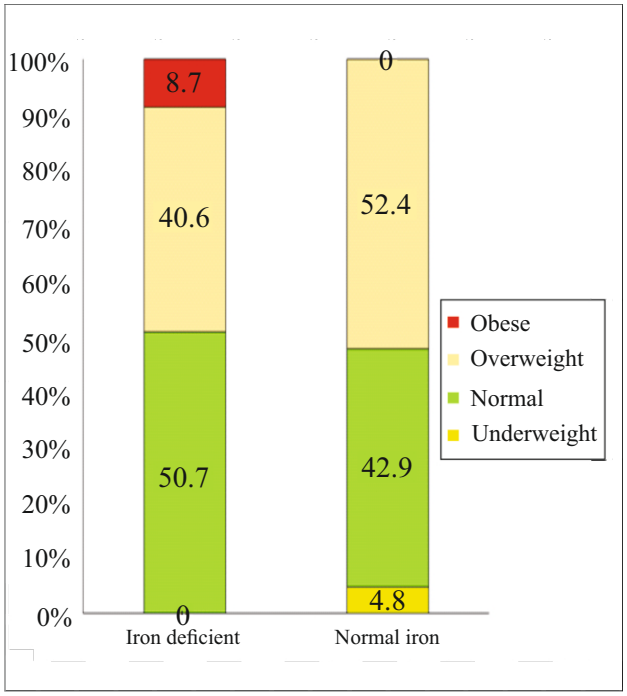

Fig. 2: Association of Iron Deficiency with Nutritional Status (BMI)

CONCLUSION

In the study undertaken at a tertiary care centre in north of India found that 76.7% of heart failure patients who had reduced ejection fraction also had iron deficiency. The absence of a quantitative, stratified assessment for iron insufficiency was one of the study's weaknesses. Further studies on a larger sample size to counter this drawback are recommended. Findings of this study have therapeutic potential and lays scaffold for further prospective studies.

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