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Original research article

A Prospective Study on Ferritin Deficiency in Heart Failure in North Karnataka Patients.

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Abstract

Introduction: Anemia is a common finding in patients with heart failure (HF). The cause for anemia is multifactorial, with iron deficiency being the most common cause. Anemia with HF is an established predictor of morbidity and mortality. Iron deficiency in systolic HF, even without anemia, has been associated with increased mortality, increased hospitalizations, and decreased functional capacity and quality of life measures.

Methods: The current study was done at the sri jayadeva institute of cardiovascular sciences hospital, Kalaburagi, Karnataka over a period of 2 years from march 2016-2018. We evaluated ID in heart failure patients. ID was defined as absolute (ferritin < 100 μg/L) or functional (transferrin Saturation index < 20% and ferritin between 100 and 299 μg/L). We evaluated if ID was a predictor of death or hospitalization due to heart failure or any cause using univariate and multivariate cox regression analysis.

Results: There were 67.5% (27/40) patients who had ID with a mean serum ferritin level of 76.4 μg/L. Of the 27 iron deficient patients, 22 (55%) had an absolute ID, and 5 had a functional ID. Eight out of 27 of the iron deficient patients were anemic (20% of the total cohort, 30% of the iron deficient patients). Anemia was seen in 6 other patients, which was possibly anemia of chronic disease. There was a trend for more advanced New York Heart Association (NYHA) class (NYHA III and NYHA IV) patients with ID (37.4% vs. 30.77%, $P = 0.697$).

Conclusion: Anaemia is a very common comorbid condition in patients of HF. The pathophysiology is diverse and includes nutritional deficiencies, loss of blood through GI tract, decreased iron absorption, and decreased release of stored iron. It is an independent predictor of reduced exercise capacity, quality of life, and recurrent hospitalizations.

Keywords: Iron, Defiance, Heart, Failure.

Introduction

Anaemia is defined by WHO as Hb < 13.0 g/dL in male adults and <12.0 g/dL in female adults.[1] It is one of the commonest associations in patients of HF[2, 3] and has been shown to be associated with increased mortality in both acute and chronic heart failure.[4, 5] The aetiology is varied, especially in countries like India where apart from other mechanisms, nutritional deficiency and worm infestations also play a part. ID has emerged as one of the most important causes of anaemia in patients of heart failure, though other causes need to be excluded as well. Iron is an essential element for humans due to its role in several functions in our bodies. There are several physiological conditions where its deficiency occurs. These are infancy, pregnancy, lactation, menstrual periods, and old age. As a majority of patients of HF are in the elderly age group, it is also important to exclude other causes of anaemia such as GI malignancies which have been reported to be present in about 10% of patients undergoing endoscopic evaluation in a large study.[6] Over the past few years, a lot of research has been carried out into ID in conditions such as chronic kidney disease, HF, chronic inflammatory diseases, and cancer, and several mechanisms have been elucidated and corrective steps identified.

MATERIALS AND METHODS:

The current study was done at the sri jayadeva instiutute of cardiovascular sciences hospital ,Kalaburagi, Karnataka over a period of 2 years from march 2016-2018. We evaluated ID in heart failure patients. ID was defined as absolute (ferritin < 100 μg/L) or functional (transferrin Saturation index < 20% and ferritin between 100 and 299 μg/L). We evaluated if ID was a predictor of death or hospitalization due to heart failure or any cause using univariate and multivariate cox regression analysis. Hematologic indices were measured in venous blood collected in EDTA tubes. The following blood biomarkers reflecting iron status were measured: Ferritin (micrograms per liter), serum iron (micrograms per liter), total iron binding capacity (micrograms per liter), transferrin (milligrams per deciliter), and transferrin saturation (TSAT). A serum ferritin in the range of 30–300 μg/L was considered to be normal.

RESULTS:

Baseline patient characteristics of the forty patients enrolled in the study are shown in Table-1. There were 67.5% (27/40) patients who had ID with a mean serum ferritin level of 76.4 μg/L. Of the 27 iron deficient patients, 22 (55%) had an absolute ID, and 5 had a functional ID. Eight out of 27 of the iron deficient patients were anemic (20% of the total cohort, 30% of the iron deficient patients)Table-2. Anemia was seen in 6 other patients, which was possibly anemia of chronic disease. Patients with ID tended to have more advanced NYHA class (NYHA III and NYHAIV) (37.4% vs. 30.77%, P = 0.697). None of the clinical variables were found to predict ID Table-3.

Table:1(Baseline patient charteristics)

Characteristics	All patients ($n=40$)	Patients with iron deficiency ($n=27$)	Patients without iron deficiency ($n=13$)	P
Age in years (SD)	46.7 (16.9)	43.7 (15.7)	52.84 (18.3)	0.11
Female (%)	9 (22.5)	7 (25.9)	2 (15.4)	0.45
LVEF % (SD)	28.22 (7.8)	28 (7.6)	28.6 (8.5)	0.83
NYHA class III and IV, *n* (%)	14 (35)	10 (37.0)	4 (30.7)	0.70
Anemia, *n* (%)	14 (35)	8 (29.6)	6 (46.1)	0.30
Diabetes (%)	7 (20.5)	6 (25)	1 (10)	0.32
Hypertension (%)	11 (32.3)	7 (29.17)	4 (40)	0.54
ACE-I and or ARB (%)	31 (88.6)	23 (92)	8 (80)	0.31
Beta blockers (%)	26 (74.3)	18 (72)	8 (80)	0.77
Loop diuretics (%)	27 (77.1)	19 (76)	8 (80)	0.80
Aldosterone antagonist (%)	25 (71.4)	18 (72)	7 (70)	0.90
Antiplatelet/ anticoagulants (%)	14 (40.0)	10 (40)	4 (40)	1.00
Statin (%)	13 (37.14)	7 (28)	6 (60)	0.07

LVEF: Left ventricular ejection fraction, SD: Standard deviation, ARB: Angiotensin receptor blocker, ACE-I: Angiotensin-converting enzyme inhibitors, NYHA: New York Heart Association

Table 2: (Hemoglobin and iron metabolism parameters)

Blood parameters	All patients ($n=40$)	Patients with iron deficiency ($n=27$)	Patients without iron deficiency ($n=13$)	P
Hb, g/dL (SD)	12.97 (1.5)	13.08 (1.6)	12.7 (1.34)	0.53
MCV (SD)	89.37 (9.6)	87.8 (10.6)	92.5 (6.21)	0.15
Ferritin, µg/L (SD)	139.3 (144.5)	76.4 (53.0)	270.0 (185.3)	<0.0001
Iron, µg/L (SD)	68.6 (30.6)	54.6 (24.9)	97.7 (18.9)	<0.0001
TSAT (%)	19.7 (10.2)	14.6 (7.1)	30.2 (7.0)	<0.0001

SD: Standard deviation, MCV: Mean corpuscular volume, TSAT: Transferrin saturation

Table:3(Clinical variables associated with iron deficiency)

Characteristics	Crude OR (95% CI)	P
Age in years	0.96 (0.92-1.00)	0.115
Female versus male	0.52 (0.09-2.94)	0.46
NYHA functional class (NYHA I and II vs. NYHA III and IV)	1.32 (0.32-5.4)	0.70
LVEF (/1%)	0.99 (0.90-1.07)	0.83
Anemia, no versus yes	0.49 (0.12-1.92)	0.3
Diabetes, no versus yes	3.00 (0.31-28.8)	0.34
Hypertension, no versus yes	0.67 (0.13-2.8)	0.54
MCV (/1 fL)	0.93 (0.84-1.02)	0.15
ACE-I and/or ARB, no versus yes	2.82 (0.34-23.9)	0.33
Beta blocker, no versus yes	0.79 (0133-4.8)	0.80
Loop diuretic, no versus yes	0.79 (0.13-4.79)	0.80
Statins, no versus yes	0.26 (0.05-1.20)	0.09
Aldosterone antagonist, no versus yes	1.10 (0.22-5.51)	0.9
Antiplatelet and/or anticoagulant, yes versus no	1.00 (0.22-4.46)	1.00

ID: Iron deficiency, OR: Odds ratio, CI: Confidence interval, LVEF: Left ventricular ejection fraction, ARB: Angiotensin receptor blocker, ACE-I: Angiotensin-converting enzyme inhibitors, NYHA: New York Heart Association, MCV: Mean corpuscular volume

DISCUSSION:

In this study, we found that ID is very common in Indian patients with systolic HF, affecting more than half the HF population. Absolute ID was more common than functional ID and patients with ID tended to have more advanced NYHA class. This study also confirmed that biochemical ID can occur in the absence of anemia. Iron is essential not only for erythropoiesis but also for several bioenergetic processes in the skeletal muscle and in the Krebs cycle. Hence, chronic ID may not only lead to anemia but, by itself, reduce exercise capacity and lead to problems, including fatigue, restless legs, memory loss, skin problems, etc. A vegetarian diet, GI losses, malabsorption, and various illnesses can be a cause of ID.

In recent years, the prevalence and prognosis of ID in chronic HF have received greater attention. There is no standard definition of ID in chronic HF, leading to a wide variation in reported prevalence. In a large observational study [9] ID was present in 37% of all systolic chronic HF patients. Another recent study, reported a prevalence of 61% among community-dwelling HF patients.[10] A study which assessed ID using bone marrow iron status, demonstrated that 73% of patients with advanced HF and anemia had depleted iron stores.[11] Nonetheless, the criteria most commonly used for detecting ID in chronic HF are a ferritin level <100 µg/L or ferritin 100–299 µg/L in combination with a TSAT <20%. Using this definition, an international pooled analysis demonstrated that the prevalence of ID was 50%.[7] In one study, 43% of anemic patients and 15% of nonanemic patients had ID. Another study found the prevalence of ID of 50% with 45.6% patients being nonanemic.[7],[8] The mechanisms of ID are multifactorial. Functional ID may occur despite adequate iron stores, whereas iron stores are depleted in absolute ID. In our study, absolute ID was the most common cause of ID, which can be explained by wide prevalent nutritional ID in India along with defective absorption in HF. Many studies have shown that ID is associated with advanced symptoms.[7],[9],[12] Our study has also shown that patients with ID have a trend to

have advanced NYHA Class. Besides being the component of hemoglobin, iron is an integral part of myoglobin and cellular respiratory chain complex. HF is a low-output state, and it requires a compensatory increase in the activity of myoglobin, hemoglobin, and respiratory chain complex for more efficient cellular utilization of oxygen. ID can compromise the function of the respiratory chain and can exacerbate the symptoms of HF even in the absence of anemia.[7]

In our study, ID was more prevalent in patients without anemia. This can be explained by the fact that anemia can occur in the absence of ID and ID anemia is the manifestation of most severe of ID (serum ferritin <15 µg/L and TSAT <10%); whereas, ID is defined as Serum ferritin <100 µg/L or TSAT <20%. Recent studies have found that different clinical characteristics have been associated with the disorder of iron metabolism in patients with HF. These include advance NYHA class, female sex, lower MCV, and anemia. However, our study failed to identify any independent predictors of ID. This might be related to the small size of our study population.

ID in India,[9],[10],[11],[12] is common, 62.9% of females below 50 years and 23.3% of males below 50 years have been reported in various surveys to be anemic. Poor Vitamin B_{12} availability in food, lack of iron and folic acid supplementation, and lack of natural sources of iron in a vegetarian diet are possible causes for ID anemia in India. Whether HF added to the burden of anemia is not possible to deduce from this study, but the high prevalence of ID provides an easily correctable factor for these patients. Oral supplementation is easy to provide and safe intravenous supplementation are now also available.[13],[14],[15],[16],[17]

Conclusion

Anaemia is a very common comorbid condition in patients of HF. The pathophysiology is diverse and includes nutritional deficiencies, loss of blood through GI tract, decreased iron absorption, and decreased release of stored iron. It is an independent predictor of reduced exercise capacity, quality of life, and recurrent hospitalizations. ID is an emerging problem in chronic HF, affecting more than half of the patients in our study sample. A decreased iron status is associated with the tendency of adverse disease severity (as assessed by NYHA functional class).

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