Original Article

Iron Deficiency in Chronic Heart Failure Patients at the University Teaching Hospital in Lusaka, Zambia

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ABSTRACT

Background: Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the muscle including myocardium and is essential for the formation of haemoglobin, myoglobin, cytochromes, cytochrome oxidase, peroxidase, and catalase. Iron deficiency (ID) often develop in chronic heart failure (CHF) patients due to depletion of iron stores, iron malabsorption and/or reduced availability of iron recycled in the reticuloendothelial system. Indeed iron content and transferrin receptor levels have been reported to be decreased in the myocardium of patients with ID. A cardinal manifestation of heart failure (both heart failure with reduced ejection fraction. HFrEF and heart failure with preserved ejection fraction, HFpEF) is impaired exercise capacity that is exaggerated in iron deficient patients. This easy fatigability is said to be a result of the reduced oxygen transport that is associated with the ID. ID leads to mitochondria and sarcomere dysfunction which reduces left ventricular functioning and hence reducing cardiac output. Reduced peak oxygen uptake has also been reported in patients with HFrEF.

Objective: To determine iron status of CHF patients at University Teaching Hospital (UTH) in Lusaka.

Methods: The study was conducted at UTH from May to August 2019. Using purposive sampling, data was collected from patients with CHF of New York Heart Association (NYHA) functional class II to IV. Information obtained included sex, age, height, weight and ejection fraction (reduced if less than 45%). From the blood samples collected, serum iron levels, transferrin levels and ferritin concentration tests were done. The chi square test and logistic regression were used to analyze iron status in CHF patients.

Results: Forty (40) patients were enrolled, 18 male and 22 female. The average age was 45.5 (19 to 60). 24 patients (60%) had (HFrEF) and 16 patients (40%) had (HFpEF). 22 patients (55%) had transferrin saturation of less than 20%, while 8 (20%) had ferritin concentration of less than 100ng/ml. Based on both factors, a total of 22(55%) patients were iron deficient. Iron deficiency was negatively associated with HFrEF ($p = 0.015$).

Conclusion: More than 55% of the participants in this study were iron deficient. However, ID may not be the primary cause of myocardial dysfunction as patients with HFrEF were less likely to be iron deficient. However, correction of ID in CHF patients in other studies has been reported to have clinical benefits. The observations of this study require further triangulation especially that the sample size was rather small.

INTRODUCTION

Iron is important for the formation of hemoglobin, myoglobin, cytochromes, cytochrome oxidase, peroxidase, and catalase. Iron plays a key role in oxygen uptake, transport, and storage, as well as

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oxidative metabolism in the muscle.[1]Heart failure patients have been reported to have abnormal cardiac structure and function causing the heart to fail to deliver oxygen at the required rate to the metabolizing tissues.[2] Heart failure (HF) is a clinical syndrome of dyspnea and diminished exercise tolerance secondary to impaired cardiac function.[3] One of the cardinal manifestation of heart failure (HF) is impaired exercise capacity that is closely related to reduced quality of life and poor outcomes that is seen to worsen if the patient is also iron deficient. Iron deficiency (ID) is a state in which available iron is insufficient to meet the requirements of the body. ID significantly reduces exercise tolerance as measured by the 6 Minutes Walking Test (MWT). Iron deficient CHF patients who were treated for iron deficiency with intravenous iron, ferric carboxymaltose, had significant improvements in the 6MWT compared with those who received placebos.[4]

ID independently predicts exercise intolerance in patients with systolic CHF.[5]The reduced exercise tolerance is as a result of the reduced oxygen transport associated with anemia; tissue iron deficiency may also play a role through reduced cellular oxidative capacity.[6] Dietary iron deficiency is associated with cardiac hypertrophy, ultrastructural changes in mitochondria and sarcomeres, and increased release of cytochrome c from mitochondria into cytosol in hearts. Iron deficiency has been associated with ultrastructural changes in cardiomyocytes including mitochondrial swelling and abnormal sarcomere structure.[7] Therefore, iron is necessary in cells that require sustained adenosine triphosphate (ATP) synthesis, such as cardiomyocytes, in addition to cells of the erythropoietic lineage.[8] In iron deficiency, structural remodelling and compensatory vascular dilatation may contribute to decreased systemic peripheral resistance and reduced afterload, which in turn increases stroke volume. Studies done in 2005 suggested that altered myocardial function develops in iron-deficient rats with changes in ventricular contractility, maximal rates of contraction and relaxation.[9]

Iron content and transferrin receptor levels were decreased in the myocardium of patients with iron deficiency anemia and advanced heart failure compared with healthy individuals, suggesting that iron depletion was associated with adverse outcomes in these patients.[4] According to the study in 2011, there was a reduction in myocardial iron content in HF compared to non-HF samples, and there was a significant reduction in the myocardial mRNA expression of transferrin receptor-1 (Tfr1), which plays a key role in cellular iron transport.[10] The inflammatory processes in CHF and their tendency to increase serum ferritin concentration cause iron-deficiency in CHF patients to be widely under recognized. Therefore, for patients with CHF, iron deficiency has been defined as ferritin less than 100 ng/mL (indicating a deficiency in iron stores), or transferrin saturation less than 20%, suggesting a disruption in iron delivery.[7]

Chronic heart failure is a common disease in Zambia particularly at the University Teaching Hospital and according to hospital records, in 2008, the proportion of deaths in heart disease patients had increased to 44.3 percent.[11] There are three categories of chronic heart failure.[1,12] The first type is heart failure with preserved ejection fraction (HFpEF), with Ejection Fraction (EF) of >50%, also referred to as diastolic failure which manifests primarily as abnormal left ventricular relaxation and increased left ventricular chamber stiffness. The second type is heart failure with reduced ejection fraction (HFrEF), ejection fraction or less than 50%, this type is of heart failure is as a result of systolic dysfunction which manifests as abnormal left ventricular contraction. The third category is heart failure with midrange ejection fraction (HFmrEF), EF 41% - 49%. However, there is ongoing debate about HFmrEF being an independent category of HF and thus a simpler criterion has been proposed that separates the types of HF into just HFrEF and HFpEF with a cut off at EF of 45% 12, 1. This is the categorization we use for the analysis of the results in

this study in order to relate the findings to a pathophysiological mechanism.

METHODOLOGY

A cross sectional observational study was done. The study population were any CHF patient between the age of 18 and 60 who came to the Medical Clinic, or were admitted in the medical wards at the UTH. The recruitment of patients into the study was done between May and August 2019. The target population was CHF patients from the study population who gave consent. Purposive sampling method was used in selecting patients. A sample size of 40 was used in this study. Blood samples were collected from patients then taken to Lancet Laboratory in Lusaka for testing of iron deficiency by doing the whole iron profile. The iron profile test measured iron level by determining the serum ferritin level, iron serum and the transferrin saturation level in blood. Iron deficiency was diagnosed for samples with serum ferritin levels of less than 100 mg/L, and a transferrin saturation (TSAT) of less than 20%.[13]

Data was collected on a hard copy data entry sheet. Each patient was assigned a patient identification number (PTID). Data was collected then transcribed onto a created electronic version of the data entry sheet on STATA and analysed. All statistical analysis were done using STATA Version 13. Serum ferritin was analysed as a dichotomous variable (< 100 μmol/L or ≥ 100μmol/L). Transferritin saturation was also analysed as a dichotomous variable (<20% or ≥ 20%). Linear regression analyses were undertaken to explore the influence of key demographic and clinical variables, including measures of iron deficiency, transferrin saturation and iron ferritin. Iron deficiency was defined as ferritin less than 100 ng/mL, or transferrin saturation less than 20%.[13]

RESULTS

Forty (40) patients were enrolled, 18 male and 22 female. The average age was 48.5 (19 to 60) years. The median height was 164cm (140cm to 183cm). Of these patients 42.5% were known hypertensives. The mean pulse rate was 87 beats/min (mean SD 9.5 beats/min). The mean weight was 65.4Kg (mean SD 18.4 kg). The mean for the systolic blood pressure was 122.0mmHg (mean SD 18.4mmHg) and the mean diastolic blood pressure was 78.3mmHg (Mean SD 16.2). 24 (60%) patients had ejection fraction < 45% (HFrEF) and 16 patients (40%) had ejection fraction >45% (HFpEF). Patient demographics and clinical findings were as shown in Table 1.0.

Table 1.0 Demographics

	n	(%)	Mean	(SD)	Median	(min, max)
Sex						
Male	18	(45.0)				
Female	22	(55.0)				
NYHF Class						
II	12	(30.0)				
III	17	(42.5)				
IV	11	(27.5)				
Known Hypertensive						
Yes	17	(42.5)				
No	23	(57.5)				
Ejection Fraction						
<45% Reduced (HFrEF)	24	(60.0)				
>45% Preserved (HFpEF)	16	(40.0)				
Age					48.0	(19, 60)
Pulse rate			86.9	(9.5)		
Height (cm)					164	(140, 183)
Weight (kg)			65.4	(18.4)		
Systolic			122.0	(18.4)		
Diastolic			78.3	(16.2)		

Table 2 shows iron levels in the chronic heart failure patients. Twenty-two (22) patients (55%) had transferrin saturation of less than 20%. While 8 (20%) had ferritin concentration of less than 100ng/ml. Considering both diagnostic factors for ID, a total of 22(55%) patients were iron deficient. Of these 45.5% had HFrEF while 54.5% had HFpEF.

Table 2 Iron levels for CHF patients at UTH.

	Ferritin.			
	= 100µmol/L		< 100µmol/L	
	n	%	N	%
Sex				
Male	16	50.0%	2	25.0%
Female	16	50.0%	6	75.0%
	Transferrin saturation			
Sex	n	<20%	n	=20%
Male	7	31.8	11	61.1
Female	15	68.2	7	38.9
	Iron deficiency (ferritin < 100ng/mL or transferrin saturation <20%)			
	Yes		No	
Sex	n	%	n	%
Male	12	54.5	6	33.3

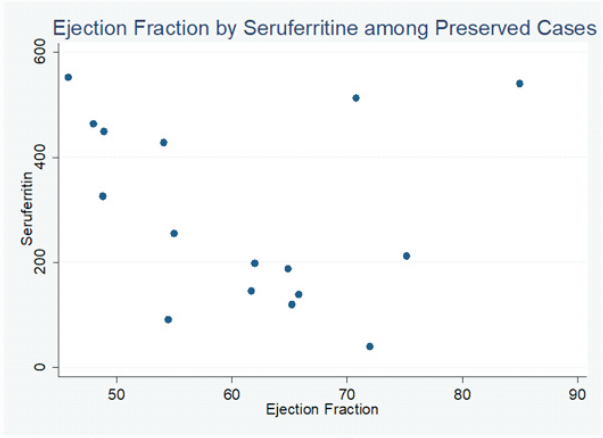
From Table 3, 12 (54.5%) of the patients with iron deficiency were males while 10 (45.5%) were females. Statistically, iron deficiency was not statistically associated with age nor NYHF class (P>0.05).

Table 3: Sex, NYHF Class, Known Hypertensive and Heart Failure by Iron Deficiency

	Iron deficiency				
	No		Yes		
	n	%	N	%	p
Sex					0.307
Male	6	33.3%	12	54.5%	
Female	12	66.7%	10	45.5%	
NYHF Class					0.475
2	7	38.9%	5	22.7%	
3	6	33.3%	11	50.0%	
4	5	27.8%	6	27.3%	
Known Hypertensive					0.234
Yes	10	55.6%	7	31.8%	
No	8	44.4%	15	68.2%	
Heart Failure					0.080
HFrEF	14	77.8%	10	45.5%	
HFpEF	4	22.2%	12	54.5%	

Graph 1 demonstrate that serum ferritin levels were not dependent on the ejection fraction in CHF with preserved ejection fraction since the points were too scattered to form the best fit line.

Graph 1.



Graph 2 demonstrate that serum ferritin levels were not dependent on the ejection fraction in CHF with reduced ejection fraction since the points were too scattered to form the best fit line.

Graph 2.

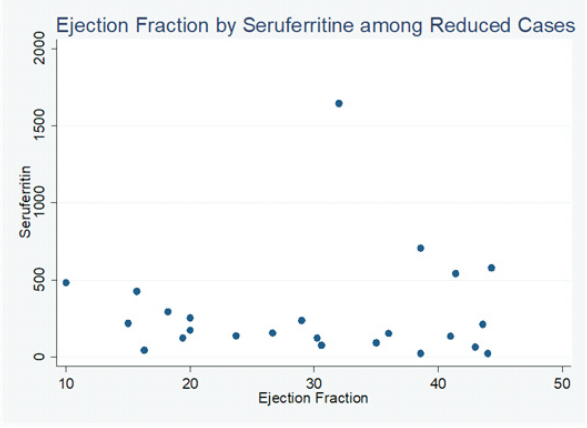


Table 4 shows that Iron deficiency was negatively associated with HFrEF (p = 0.015). While Iron deficiency can occur both in patients with HFrEF and HFpEF, patients with HFrEF were less likely to be iron deficient.

Table 4 Multivariate logistic regression model of demographics by iron deficiency.

		95%CI				95%CI		
	OR	Lower	Upper	p	AOR	Lower	Upper	p
Sex								
Male	2.400	0.661	8.720	0.184	8.471	0.566	126.849	0.122
Female (Ref)								
NYHF Class								
2	0.595	0.114	3.102	0.538	0.979	0.103	9.327	0.985
3	1.528	0.325	7.188	0.592	0.283	0.023	3.433	0.322
4 (Ref)								
Known hypertensive								
Yes	0.373	0.103	1.359	0.135	0.275	0.037	2.050	0.208
No (Ref)								
Heart Failure								
HFrEF	0.238	0.059	0.958	0.043	0.034	0.002	0.517	0.015
HFpEF (Ref)								
Age	1.012	0.957	1.071	0.671	1.040	0.941	1.150	0.440
Pulse rate	0.991	0.927	1.060	0.795	0.924	0.830	1.029	0.151
Height	22.730	0.027	19.254	0.363	14.232	0.128	15.343	0.095
Weight	1.002	0.968	1.037	0.903	0.984	0.917	1.056	0.655
Systolic	0.978	0.947	1.009	0.164	1.016	0.948	1.089	0.648
Diastolic	0.967	0.927	1.010	0.128	0.911	0.819	1.014	0.090

DISCUSSION

Iron deficiency has been widely reported in HF patients and correction of the iron deficiency in these patients has been shown to have beneficial effects which have been attributed to improvement in myocardial contractility[7]. In a recent study on dietary iron deficiency in rats, it was demonstrated that dietary iron deficiency was actually associated with myocardial hypertrophy and ultrastructural changes in mitochondria and sarcomeres[9]. These findings supported the previous findings where the investigators showed that altered myocardial function develops in iron deficient rats with changes in ventricular contractility, action potentials and L-type Ca+ currents[14]. Some studies have shown significant improvements in left ventricular function of iron deficient HFrEF patients after three months of intravenous iron therapy[15]. However, according to our study, ID may not be the primary cause of myocardial dysfunction in patients of CHF as patients with HFrEF were actually less likely to be iron deficient.

This study demonstrated that iron deficiency was not associated with age and gender just like seen in other studies[16]. In the landmark randomized trial of iron repletion, HFrEF patients were observed to have decreased NYHA class and they demonstrated improvements after iron supplements[7] but in this study, ID was observed with similar prevalence in all the NYHA classes (II – IV). Recent studies by Okonko et al and Jankowska et al also found NYHA class to be an independent and even inverse predictor of impaired iron status[5,17,18]. Although NYHA class has been used to describe the severity of symptoms of HF patients and exercise tolerance, symptom severity has been shown to correspond rather poorly with many measures of left ventricular functioning[12].

This study showed that 55% of the chronic heart failure patients were iron deficient. These findings were similar to the findings in the study done in 2010 were it as estimated that iron deficiency affects between 37% and 61% of patients with chronic heart failure[5]. Other studies reported an iron deficiency prevalence of 61% among community-dwelling HF patients[19].

The prevalence and possible consequences of ID complicating CHF syndrome has only recently

drawn attention. Data on the epidemiology and pathophysiology of ID in CHF are scarce. Iron deficiency has usually been considered in the context of anaemia, both generally and in patients with CHF. However, recent studies have showed that, ID is a stronger predictor for mortality independently of other well-established outcome predictors including anemia[4].

In this study, 55% of the CHF patients had transferrin saturation of less than 20% while only 20% of them had ferritin concentration of less than 100ng/ml. This may be related to the processes of inflammation that have been reported in CHF where the higher serum ferritin levels than expected were recorded and attributed to inflammatory mediators[7]. Unlike serum ferritin level, the transferrin saturation is not affected by states of inflammation. Thus, it is a more accurate measure of total body iron than the serum iron concentration. However it does not directly measure the iron stores[13]. In this study, both measures of iron ferritin and transferrin saturation were used to qualify patients to be iron deficient as recommended[7].

Patients with CHF are prone to become iron deficient as a consequence of depletion of iron stores (absolute ID) or more frequently as a result of impaired iron metabolism in the course of inflammatory processes characterizing CHF (functional ID)[16]. In CHF, there is an activation of pro-inflammatory cytokines that block intestinal absorption of iron and divert iron from the circulation into the reticuloendothelial system, causing reticuloendothelial block[13]. Hepcidin, a small hepatic peptide, secreted in response to pro-inflammatory cytokines, seems to play a key role in the control of these processes. Decreased intestinal iron absorption together with its accumulation within the reticuloendothelial stores reduces iron availability to its target tissues and organs. Thus, functional ID (depletion of iron available to the tissues) may occur despite adequate iron stores in the body, in contrast to absolute ID (depletion of iron stores) where the body iron stores are significantly depleted. In this study, the applied definition of ID takes into consideration both serum ferritin (≤ 100 mg/L) and transferrin saturation (≤ 20%). Similar definitions have been applied in recent intervention trials which showed that repletion of ID resulted in improvement in exercise capacity and quality of life [20,7,22,12,16].

STUDY LIMITATIONS

This study was time limited to fit into the academic study period thus included a small sample size. A major limitation of this investigation was that it was an 'uncontrolled comparison' study whose findings are essentially based upon those observed within the same group. Also that, only data from a single measurement in time were available thus effects of changes in iron status over time cannot be inferred. Better serum markers need to be identified to better reflect iron status in comparison with the criterion standard of bone marrow iron staining. A general lack of local research evidence on iron deficiency in CHF and in the Zambian population in general was a challenge in data analysis. Thus more research in this field is encouraged.

CONCLUSION

Iron deficiency is indeed an emerging problem in patients with chronic heart failure and more than 55% of the participants in this study were iron deficient. However, the pathoaetiological relationship to the causation of heart failure is yet to be elucidated. While there have been clinical benefits reported in CHF patients where iron deficiency was corrected, the pathophysiological mechanism for this improvement have not been clearly described. Iron deficiency per se may not be the primary cause of myocardial dysfunction in our study participants as patients with HFrEF were less likely to be iron deficient. However, the observations of this study require further triangulation especially that the sample size was relatively small. The results of clinical trials should encourage cardiologists to consider iron deficiency as a therapeutic target in Chronic Heart Failure.

DECLARATIONS

Approval to conduct the research was given by the University of Zambia biomedical research ethics committee with a reference number 016-03-19. Consent was obtained from the participants prior to data collection. This study was self-sponsored. Acknowledgement goes to Musonda Patrick and Mr John Banda for helping with statistics, the Nurses and Doctors at UTH cardiology department, doctor Sinkala Annel and Lancet Laboratory.

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