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Association of Iron Deficiency Anemia with the Development and Progression of Heart Failure

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ABSTRACT

***Background**: In addition to hematopoiesis, iron plays an essential role in numerous biological processes that maintain homeostasis. Patients with heart failure (HF) are prone to developing iron deficiency (ID). **Aims of the Study**: To investigate the prevalence of iron deficiency and factors affecting this deficiency in patients with heart failure.*

***Patients and Methods**: This cross-sectional study included 100 patients diagnosed with HF at admission (50 men and 50 women). Another 100 age- and sex-matched apparently healthy subjects were recruited to represent the control group. The following parameters were investigated for each participant: serum ferritin, transferrin saturation, haemoglobin (Hb), complete blood count, and hematocrit.*

***Results:** Patients with HF showed significantly higher frequencies of absolute ID, anaemia, and ID anaemia (41%, 52%, and 34%, respectively) than controls (17%, 17%, and 8%, respectively). In multivariate analysis, the female gender (OR= 2.81, 95%CI= 1.18-14.8, p= 0.028), anaemia (OR= 9.49, 95%CI=1.88-18.73, p<0.001), and mean cell volume (MCV)< 80 (OR= 3.8, 95%CI= 1.07- 22.34, p= 0.044) were independent predictors of ID in patients with HF.*

***Conclusions**: Absolute ID is much more prevalent among HF patients. Each of the female gender, anaemia, and low MCV is an independent factor that could predict the occurrence of ID. It is recommended to assess iron levels in each patient with HF, and to provide appropriate iron supplementation to correct ID when present.*

***Keywords:** Iron deficiency (ID); anemia; Development and Progression; heart failure (HF).*

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Introduction

Heart failure (HF) is a prevalent and growing condition, with its burden expected to increase by up to 50% by 2030 due to population ageing and improved survival from coronary artery disease [1]. Despite therapeutic advances, HF remains associated with significant morbidity and mortality, with 1-year mortality rates of 25–35% following hospitalization and persistent limitations in functional capacity [2].

Iron is essential for cellular metabolism; however, iron deficiency (ID) affects up to one-third of the global population and is particularly common in chronic inflammatory diseases such as HF [3,4]. ID can occur independently of anaemia and is classified as absolute (ferritin <100 µg/L) or functional (ferritin 100–300 µg/L with transferrin saturation <20%), reflecting impaired iron utilisation [5].

ID is highly prevalent in HF, affecting 35–50% of patients and representing the leading cause of anaemia in this population [6,7]. Importantly, bone marrow studies suggest that ID may be underestimated when relying solely on serum markers [8]. Patients at higher risk include older individuals, women, and those with more advanced HF, with strong associations observed with NYHA class, NT-proBNP, and inflammatory markers [2,9,10]. In contrast, common cardiovascular medications do not appear to affect iron status significantly, suggesting that mechanisms beyond overt blood loss contribute to ID in HF [2].

Therefore, the current study aims to investigate the prevalence of iron deficiency and the factors that affect it in patients with heart failure.

Patients and Methods

Study Setting and Design: This is a cross-sectional study conducted at Medical City-Baghdad Teaching Hospital from March 2019 to February 2020. A total of 100 patients diagnosed with HF on admission (50 men and 50 women) attending this hospital were recruited for this study. Another 100 age- and sex-matched apparently healthy subjects were recruited to represent the control group.

Inclusion Criteria: All adult patients with a documented history of HF of ≥6 months;

Exclusion Criteria: any acute/chronic illness that might influence iron metabolism (including known malignancy, infection, severe renal disease requiring dialysis, and hematological diseases); acute coronary syndrome; any anemia or/and ID treatment either at the time of the study or in the past 12 months; pregnancy; malignant disorder; poor nutritional state and active bleeding or history of bleeding disorder.

Ethical Considerations

Ethical approval for this study was obtained from the Scientific and Ethics Committee of Medical City–Baghdad Teaching Hospital before data collection.

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Participant confidentiality was strictly maintained, and all data were handled securely and not disclosed to unauthorised parties. Informed consent was obtained from all participants after the study objectives were explained.

Investigations

Approximately 5 mL of venous blood was collected from each participant to measure serum ferritin, transferrin saturation, haemoglobin (Hb), complete blood count, and hematocrit, all of which were analysed in the hospital laboratory. Iron deficiency (ID) was defined as ferritin <100 µg/L, or 100–299 µg/L with transferrin saturation <20%, according to FAIR-HF criteria and ESC guidelines [12]. Anaemia was defined according to WHO criteria as Hb <13 g/dL in men and <12 g/dL in women [13].

Data Collection

A preformed questionnaire was used to obtain information on patients' socio-demographic data, detailed history and physical examination, body mass index (BMI), smoking habits, and the presence of DM.

Statistical analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were expressed as mean±SD and analysed with Student's t-test. Categorical variables were expressed as numbers and percentages and analysed with the Chi-square test. Univariate and multivariate logistic regression were used to assess the association between each factor and ID. From this test, the odds ratio (OR) and its 95% confidence interval (95% CI) were calculated. A p- value less than 0.05 was considered to indicate a statistically significant difference.

Results

Demographic and Clinical Characteristics of the Study Population

Mean age of the HF patients was 61.77±9.6 years, which did not differ significantly from that of healthy controls (59.6±12.7 years). The male-female ratio in the two groups was identical (1:1); however, 36% of patients were ex/current smokers, compared with 22% of controls, with a significant difference (p=0.029). Mean BMI in patients and controls was 26.71±4.7 kg/m^2 and 27.14±6.12 kg/m^2, respectively, with no significant difference. Likewise, there was no significant difference between the two groups in the frequency of diabetes (29% versus 21%).

Table 1: Patients' characteristics and clinical data (n=100)

Variables	Patients (n=100)	Controls (n=100)	p-value
Age, years (mean±SD)	61.77±9.6	59.6±12.7	0.089
Gender Male Female	 50(50%) 50(50%)	 50(50%) 50(50%)	1.0
Smoking Never Ex/current	 64(64%) 36(36%)	 78(78%) 22(22%)	**0.029**
BMI, kg/m^2	26.71±4.7	27.14±6.12	0.289
Diabetes mellitus No Yes	 71(71%) 29(29%)	 79(79%) 21(21%)	0.191
Hb, g/dl (mean±SD)	12.43±3.9	13.51±4.22	**0.01**
MCV, fl (mean±SD)	84.2±6.6	89.8±7.82	**<0.001**
MCH, pg (mean±SD)	27.8±2.1	30.3±3.3	**<0.001**
MCHC, g/dl (mean±SD)	32.8±4.3	34.2±4.9	**<0.001**

SD: standard deviation, BMI: body mass index, Hb: haemoglobin, MCV: mean cell volume, MCH: mean cell haemoglobin, MCHC: mean cell concentration.

There was a reduction in all included haematological indices in patients compared with controls, with highly significant differences (Table 1). Mean Hb%, MCV, MCH and MCHC in patients was 12.43±3.9 g/dl, 84.2±6.6 ft, 27.8±2.1 pg and 32.8±4.3 g/dl, respectively compared with 13.51±4.22 g/dl, 89.8±7.82 fl, 30.3±3.3 pg and 34.2±4.9 g/dl, respectively in controls.

The Frequency of Anaemia and Iron Deficiency

Using WHO criteria (Hb <13 g/dL in men, <12 g/dL in women) and absolute iron deficiency defined as ferritin <100 µg/mL, we compared patients and controls. Absolute iron deficiency was significantly more frequent in patients than in controls (41% vs. 17%, p<0.001). Anaemia (52% vs 17%) and iron-deficiency anaemia (34% vs 8%) were also significantly higher in patients. Iron deficiency without anaemia was similar between groups (7% vs. 5%). Anaemia without iron deficiency was twice as common in patients (18% vs. 9%), but the difference was not significant.

Table 2: The frequency of absolute iron deficiency, anaemia, iron deficiency anaemia, iron deficiency without anaemia, and anaemia without iron deficiency in patients and controls

Variables	Patients (n=100)	Controls (n=100)	p-value
Absolute iron deficiency No Yes	 59(59%) 41(41%)	 87(87%) 13(13%)	**<0.001**
Anemia No Yes	 48(48%) 52(52%)	 83(83%) 17(17%)	**<0.001**
Iron deficiency anaemia No Yes	 66(66%) 34(34%)	 92(92%) 8(8%)	**<0.001**
Iron deficiency without anaemia No Yes	 93(93%) 7(7%)	 95(95%) 5(5%)	0.552
Anaemia without iron deficiency No Yes	 82(82%) 18(18%)	 91(91%) 9(9%)	0.063

Predictor of Iron Deficiency in Patients with Heart Failure

HF patients were divided into two groups: iron-deficient (ID, n=41) and non-iron-deficient (non-ID, n=59). Univariate analysis identified five significant predictors of ID: female sex (65.85% in ID vs. 38.98% in non-ID, p=0.008), smoking history (48.78% vs. 27.12%, p=0.026), presence of anaemia (87.8% vs. 27.12%, p<0.001), low MCV (<80 fL; 58.54% vs. 37.29%, p=0.036), and diuretic use (63.41% vs. 42.37%). These factors were significantly associated with iron deficiency in HF patients.

Table 3: Univariate analysis for predictors of iron deficiency anaemia in patients with heart failure

Variables	Iron-deficient patients (n=41)	Non-Iron-deficient patients (n=59)	P- value
Age, years < 60 ≥60	 19(46.34%) 22(53.66%)	 23(38.98%) 36(61.02%)	0.463
Gender Male Female	 14(34.15%) 27(65.85%)	 36(61.02%) 23(38.98%)	**0.008**
Smoking Never Ex/current	 21(51.22%) 20(48.78%)	 43(72.88%) 16(27.12%)	**0.026**
BMI, kg/m^2 < 25 ≥ 25	 24(58.54%) 17(41.46%)	 24(40.68%) 35(59.32%)	0.155
Diabetes mellitus No Yes	 25(60.98%) 16(39.02%)	 46(77.97%) 13(22.03%)	0.066
Anemia No Yes	 5(12.2%) 36(87.8%)	 43(72.88%) 16(27.12%)	**<0.001**
MCV, fl ≥ 80 < 80	 17(41.36%) 24(58.54%)	 37(62.71%) 22(37.29%)	**0.036**
MCH, pg ≥ 27 < 27	 20(48.78%) 21(51.22%)	 28(47.46%) 31(52.54%)	0.896
MCHC, g/dl ≥ 30 < 30	 22(53.66%) 19(46.34%)	 33(55.93%) 26(44.07%)	0.822
Treatment ‡ ACE inhibitors Anticoagulant Beta blockers Diuretic agent	 23(56.1%) 8(19.51%) 18(43.9%) 26(63.41%)	 31(52.54%) 11(18.64%) 19(32.2%) 25(42.37%)	 0.726 0.884 0.233 **0.038**

BMI: body mass index, Hb: haemoglobin, MCV: mean cell volume, MCH: mean cell haemoglobin, MCHC: mean cell haemoglobin concentration. ‡ A patient can have more than one drug.

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In multivariate analysis (Table 4), three independent predictors of iron deficiency (ID) remained significant in HF patients. Female sex was associated with a higher odd of ID than male sex (OR = 2.81, 95% CI = 1.18–14.8, p = 0.028). Anaemia showed the strongest association (OR = 9.49, 95% CI = 1.88–18.73, p < 0.001). Low MCV (<80 fL) was also significantly associated with ID (OR = 3.8, 95% CI = 1.07–22.34, p = 0.044). Smoking and diuretic use lost their significance after adjustment. (Figure 3).

Table 4: Multivariate analysis for predictors of iron deficiency anaemia in patients with heart failure

Variables	p-value	OR(95%CI)
Age, years		
< 60	0.511	1.0(Reference)
≥60		0.84(0.44-11.92)
Gender		
Male	**0.028**	1.0(Reference)
Female		2.81(1.18-14.8)
Smoking		
Never	0.093	1.0(Reference)
Ex/current		2.23(0.89-12.52)
BMI, kg/m²		
< 25	0.443	1.0(Reference)
≥ 25		0.92(0.48-9.21)
Diabetes mellitus		
No	0.086	1.0(Reference)
Yes		1.92(0.86-9.17)
Anemia		
No	**<0.001**	1.0(Reference)
Yes		9.49(1.88-18.73)
MCV, fl		
≥ 80	**0.044**	1.0(Reference)
< 80		3.8(1.07- 22.34)
MCH, pg		
≥ 27	0.791	1.0(Reference)
< 27		1.18(0.811.97)
MCHC, g/dl		
≥ 30	0.698	1.0(Reference)
< 30		2.21(0.78-10.36)
Treatment ‡		
ACE inhibitors	0.811	1.0(Reference)
Anticoagulant	0.911	1.21(0.62-11.8)
Beta blockers	0.781	0.76(0.44-8.17)
Diuretic agent	0.059	3.11(0.96-13.84)

BMI: body mass index, Hb: haemoglobin, MCV: mean cell volume, MCH: mean cell haemoglobin, MCHC: mean cell haemoglobin concentration. OR = odds ratio, CI = confidence interval, ‡ A patient can have more than one drug.

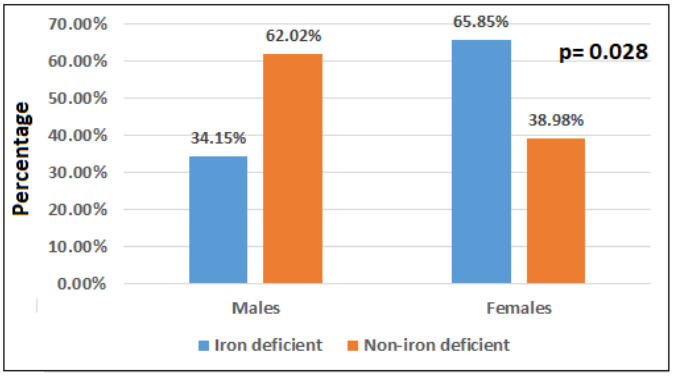

Figure 1: Gender distribution in iron-deficient and non-iron-deficient patients

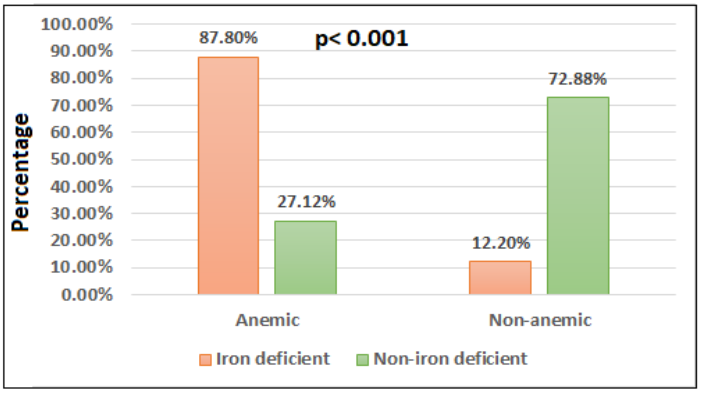

Figure 2: Anaemia frequency in iron-deficient and non-iron-deficient patients

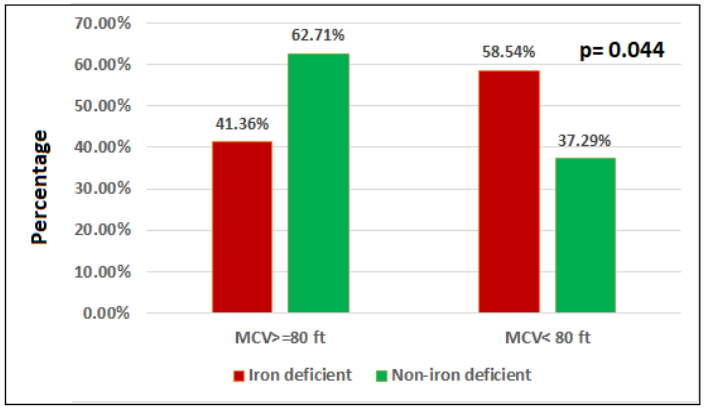

Figure 3: MCV variation in iron-deficient and non-iron-deficient patients

Discussion

In this study, absolute iron deficiency (ID) prevalence was 41% in patients vs. 17% in controls (p<0.001), consistent with prior HF studies. Fonseca *et al.* [14] reported an ID rate of 41% in Portuguese HF patients, while other studies reported ID prevalence ranging from 13.7% [15] to 63% [16]. Using bone marrow iron staining as the gold standard, Nanas et al. [17] found an ID of 73% in advanced HF with anaemia. In contrast, general population studies report much lower ID rates (e.g., 4.7–6.1% in French adults [18]), highlighting the impact of definition criteria, study design, and comorbidities.

The HF-ID relationship is bidirectional. HF may cause ID via: (1) depletion of iron stores (absolute ID), or (2) inflammation-driven impaired iron metabolism (functional ID) [19,20], with hepcidin playing a key role [21,22]. Conversely, ID may contribute to HF development by impairing mitochondrial energy production in cardiomyocytes [23], reducing exercise capacity [24-26], and altering myocardial transferrin receptor expression [27,28].

Multivariate analysis identified female sex, anaemia, and low MCV as independent predictors of ID. Similar findings were reported by Klip et al. [2] (female sex, lower MCV, anaemia) and Jankowska et al. [10] (female sex, advanced NYHA). No association was found between ID and antiplatelet/anticoagulant use [9], in contrast to ACEI-anaemia links. Predictors may vary by sex [38] and are influenced by genetic (e.g., TMPRSS6 mutations and dietary factors (e.g., Mediterranean diet vs Northern European iron intakes [29]).

Conclusions: Absolute iron deficiency is significantly more prevalent in patients with heart failure than in healthy controls. Female gender, anaemia, and low mean corpuscular volume are independent predictors of iron deficiency in these patients. Furthermore, iron deficiency may contribute to the pathogenesis of heart failure.

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