Absolute and Functional Iron Deficiency Is a Common Finding in Patients With Heart Failure and After Heart Transplantation

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ABSTRACT

Background. Anemia is relatively common in patients with heart failure and heart transplant recipients. Both absolute and functional iron deficiency may contribute to the anemia in these populations. Functional iron deficiency (defined as ferritin greater than 200 ng/mL with TSAT (Transferrin saturation) less than 20%) is characterized by the presence of adequate iron stores as defined by conventional criteria, but with insufficient iron mobilization to adequately support. The aim of this study was to determine prevalence of absolute and functional iron deficiency in patients with heart failure (n = 269) and after heart transplantation (n = 130) and their relation to parameters of iron status and inflammation.

Methods. Iron status, complete blood count, and creatinine levels were assessed using standard laboratory methods. C-reactive protein, hepcidin and hemojuvelin were measured using commercially available kits.

Results. Absolute iron deficiency was present in 15% of patients with heart failure and 30% in heart transplant recipients, whereas functional iron deficiency was present in 18% of patients with heart failure and 17% in heart transplant recipients. Functional iron deficiency was associated with significantly higher C-reactive protein and hepcidin levels in heart failure patients, and higher hepcidin and lower estimate glomerular filtration rates in heart transplant recipients. Prevalence of anemia (according to the World Health Organization) was significantly higher in heart transplant recipients (40% vs 22%, $P < .001$), they were also younger, but with worse kidney function than patients with heart failure.

Conclusions. Both absolute and functional iron deficiency were present in a considerable group of patients. This population should be carefully screened for possible reversible causes of inflammation.

THE MAJOR indication for heart transplantation is chronic heart failure (CHF) due to different causes. Patients with CHF are prone to anemia and iron metabolism disturbances [1]. In 2000, the American Society of Transplantation [2] endorsed the initial World Health Organization (WHO) definition [3] with hemoglobin levels less than 13 g/dL in men and less than 12 g/dL in women. Anemia is very often associated with kidney dysfunction [4]. One of the major reasons for post-transplantation anemia is iron deficiency, which is relatively common among solid organ transplant recipients [5]. Our current understanding of iron metabolism and its deficiency is based on the biology of a number of critical proteins. Hepcidin has emerged as a key regulator of iron homeostasis [6]. Hepcidin is a small defensin-like peptide whose production by hepatocytes is modulated in response to anemia, hypoxia, or inflammation [6]. Disturbed iron metabolism at an early stage of heart

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failure (HF) was detected by increased circulating hepcidin, which subsequently decreases with progression of the disease, and is accompanied by iron-restricted compromised erythropoiesis. Both absolute and functional iron deficiency may contribute to the anemia in these populations. Functional iron deficiency (defined as ferritin levels greater than 200 ng/mL with TSAT (transferrin saturation) less than 20%) is characterized by the presence of adequate iron stores as defined by conventional criteria, but with insufficient iron mobilization to adequately support [1,7]. The aim of this study was to determine the prevalence of absolute and functional iron deficiency in HF and after heart transplantation and their relation to parameters of iron status and inflammation.

PATIENTS AND METHODS

We analyzed 130 patients who underwent their first orthotopic heart transplantation (OHT) at Jagiellonian University, Cracow, Poland (32 females). Before OHT in all the patients, the serum creatinine level was below 1.8 mg/dL. The immunosuppressive regimen of prevalent patients consisted of calcineurin inhibitor in combination with mycophenolate mofetil/azathioprine and everolimus or sirolimus or prednisone. All of them maintained sufficient and stable graft function and showed no clinical signs of rejection. We also included 269 consecutive patients (87 females) with HF who were admitted to the Department of Invasive Cardiology for percutaneous coronary interventions. Clinical and biochemical data of both groups are in Table 1. The criteria for patients with HF to be included in the study were according to European Society of Cardiology guidelines from 2012 [8]. Absolute iron deficiency was diagnosed with higher cut-off ferritin values (ie, <100 μg/L) while functional iron deficiency was diagnosed with normal serum ferritin (100–300 μg/L) and low transferrin saturation (<20%). Such a definition of iron deficiency has been applied in HF syndrome, including clinical trials [9]. All subjects gave informed consent, and the protocol was approved by the local ethics committee. Blood was drawn in the morning when patients appeared for routine office assessment after an overnight fast. Glomerular filtration rates (GFRs) were estimated using the simplified Modification of Diet in Renal Disease formula (estimated GFR [eFGR] = 186.3 × serum creatinine (mg/dL)$^{-1.14}$ × age$^{-0.203}$ × 0.742 if female, and × 1.21 if Afro-American) [10]. Complete blood count, urea, serum lipids, fasting glucose, and creatinine levels were studied by standard laboratory method in the central laboratory of the hospital. Hepcidin was assayed by enzyme immunoassay using commercially available kits from Bachem (St Helens, United Kingdom). Hemojuvelin was measured using kits from R&D (Abington, United Kingdom). Data expressed as mean values ± SD were analyzed using Statistica 10.0 computer software (Tulsa, Oklahoma, United States). The Mann-Whitney rank sum U test or Student *t* test was used to compare differences between groups with $P < .05$ considered statistically significant.

RESULTS

Absolute iron deficiency was present in 15% of patients with HF and 30% in heart transplant recipients, whereas functional iron deficiency was present in 18% of patients with HF and 17% in heart transplant recipients. Functional iron deficiency was associated with significantly higher C-reactive protein (−8.54 [0.8; 43.8 mg/L] vs 2.91 [0.01–14.1] mg/L; $P < .001$) and hepcidin levels (56.32 [21.45; 119.38] ng/mL vs 25.43 [0.48; 42.67] ng/mL; $P < .01$) in HF patients, higher hepcidin (35.32 [19.54; 73.52] ng/mL vs 16.76 [0.74; 34.32] ng/mL; $P < .01$) and lower eGFR (42.41 ± 26.21 mL/min/1.72 m^2 vs 61.41 ± 29.65 mL/min/1.72 m^2; $P < .05$) in heart transplant recipients. Prevalence of anemia (according to WHO, ie, hemoglobin levels less than 13 g/dL in men and less than 12 g/dL in women) was significantly higher in heart transplant recipients (40% vs 22%; $P < .001$%), they were also younger (56.76 ± 15.67 years vs 67.82 ± 12.54 years; $P < .05$), but with worse kidney function (50.21 ± 30.32 mL/min/1.72 m^2 vs 82.21 ± 23.54 mL/min/1.72 m^2) than patients with HF.

Table 1. Clinical and Biochemical Data of the Heart Allograft Recipients and Patients With Chronic Heart Failure

	OHT n = 130	CHF n = 269
Age (y)	54.54 ± 13.98	61.65 ± 12.65*
Time after transplantation (mo)	101 ± 53	NA
Hemoglobin (g/dL)	12.96 ± 2.14	13.21 ± 1.59
Erythrocyte count (×10^{12}/μL)	4.65 ± 0.71	4.67 ± 0.59
Creatinine (mg/dL)	1.68 ± 1.08	1.02 ± 0.26†
eGFR – MDRD (mL/min)	55.32 ± 28.32	90.41 ± 20.21†
EF (%)	56.31 ± 11.21	38.69 ± 15.32*
CRP (mg/L)	8.04 (0.01–101.0)	4.78 (0.01–43.8)†
Iron (μg/dL)	94.32 ± 33.98	82.54 ± 41.93
TSAT (%)	28.91 ± 13.81	27.01 ± 14.62
Ferritin (μg/L)	134.6 (3.32; 854.3)	179.2 (5.43; 781.2)
sTfR (nmol/L)	31.65 ± 13.45	22.02 ± 9.43*
Hepcidin (ng/mL)	21.96 (0.74; 73.52)	46.52 (0.48; 119.38)‡
Hemojuvelin (ng/mL)	453.43 (43.40; 7078.32)	231 (21.56; 1056.43)†

Data given are means ± SD or median and minimum and maximum.
Abbreviations: OHT, heart allograft recipients; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; EF, ejection fraction; CRP, C-reactive protein; TSAT, transferrine saturation; sTfR, soluble transferrine receptor.
*$P < .05$.
†$P < .001$ versus CHF.
‡$P < .01$.

DISCUSSION

The role of iron deficiency in HF has been the subject of many recent reviews during the last 2 years [11,12]. However, clinical evidence on the incidence of iron deficiency in HF patients is scarce. When iron deficiency in HF is defined as either a serum ferritin of <100 μg/L or a serum ferritin of 100–300 μg/L along with a percentage of transferrin saturation (serum iron divided by transferrin levels multiplied by 100% transferrin saturation) of <20%, approximately 60% of the anemic patients (24% of all HF patients) and approximately 40% of the non-anemic patients (also 24% of all HF patients) have iron deficiency [13,14]. Most available studies have presented a traditional