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Bone marrow iron depletion is common in patients with coronary artery disease

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ABSTRACT

Background/objectives: Iron deficiency (ID) may be an important, treatable co-morbidity complicating cardiovascular diseases, but considerable uncertainty exists about the diagnostic accuracy of blood tests. Accordingly, we investigated the relationship between blood tests for ID and iron stores in bone marrow aspirates, the diagnostic *gold-standard* for ID, in patients with stable coronary artery disease (CAD).
Methods: Bone marrow aspirates were obtained from 65 patients with stable CAD undergoing cardiac surgery and 10 healthy controls. ID was defined as depleted extracellular iron stores (0–1 grade according to Gale scale) accompanied by ≤10% of erythroblasts containing iron.
Results: Bone marrow ID was found in 31 (48%) patients with CAD but in none of the controls ($p < 0.01$). Amongst patients with CAD, ID was present in 10 of 16 (63%) with and 21 of 49 (43%) without anaemia ($p = 0.17$). The clinical profiles of patients with and without ID were similar. Of circulating biomarkers of ID, serum soluble transferrin receptor had the strongest association with bone marrow ID (area under curve: 0.876 ± 0.048, 95% confidence interval: 0.762–0.948, for cut-off of ≥1.32 mg/L—sensitivity: 67%, specificity: 97%).
Conclusions: Almost half of patients with stable CAD have profound bone marrow iron depletion that can be accurately assessed non-invasively using serum soluble transferrin receptor.

1. Introduction

Iron deficiency (ID) may be an important co-morbidity in patients with either high cardiovascular risk (obesity, metabolic syndrome, diabetes mellitus, elderly) [1–4], clinically overt coronary artery disease (CAD) [3,5] or heart failure (HF) [6–11]. Intravenous iron supplements given to patients with HF who have blood tests indicating ID improves symptoms, exercise capacity and quality of life, and appears safe [12–14].

However, accurate diagnosis of ID, and therefore which patients will benefit from therapy, remains challenging. Assessment of iron stores directly in bone marrow aspirates is the *gold standard* for evaluating ID [15–18], but sampling can be painful, requires expertise and is time consuming, and therefore is not a suitable method for excluding or confirming ID in routine clinical practice. The diagnosis of ID in routine clinical practice and cardiovascular research is typically based on plasma/serum biomarkers of iron metabolism, usually ferritin, iron and transferrin saturation (Tsat) [15–17,19,20]. However, low-grade inflammation commonly accompanies cardiovascular diseases, which may modify the production of several markers of ID, reducing their sensitivity and reliability to detect ID [15,21,22].

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Table 1
Baseline clinical and laboratory characteristics of patients with stable coronary artery disease by bone marrow iron status.

Variables	All patients with CAD ($n = 65$)	Patients with CAD and ID in bone marrow ($n = 31$; 48%)	Patients with CAD without ID in bone marrow ($n = 34$; 52%)
Demographic and clinical characteristics			
Age, years	64 ± 8	63 ± 8	65 ± 8
Men, *n* (%)	59 (91%)	28 (90%)	31 (91%)
BMI, kg/m^2	27.9 ± 4.0	27.9 ± 4.3	27.9 ± 3.7
Systolic BP, mm Hg	129 ± 22	127 ± 20	131 ± 23
Diastolic BP, mm Hg	69 ± 10	66 ± 10	72 ± 10
HR, bpm	72 ± 14	74 ± 16	71 ± 11
LVEF, %	48 ± 14	45 ± 11	50 ± 16
Co-morbidities			
Previous MI, yes, *n* (%)	31 (48%)	16 (52%)	15 (44%)
Hypertension, yes, *n* (%)	57 (88%)	26 (84%)	31 (91%)
Atrial fibrillation, yes, *n* (%)	15 (23%)	9 (29%)	6 (18%)
Diabetes mellitus, yes, *n* (%)	27 (42%)	14 (45%)	13 (38%)
COPD, yes, *n* (%)	4 (6%)	2 (6%)	2 (6%)
Treatment			
ACE-I or/and ARB, yes, *n* (%)	55 (85%)	27 (87%)	28 (82%)
β-blocker, yes, *n* (%)	58 (89%)	28 (90%)	30 (88%)
Ca^{2+}-channel blocker, yes, *n* (%)	9 (14%)	4 (13%)	5 (15%)
MRA, yes, *n* (%)	14 (22%)	6 (19%)	8 (24%)
Diuretic, yes, *n* (%)	31 (48%)	18 (58%)	13 (38%)
Statin, yes, *n* (%)	63 (97%)	29 (94%)	34 (100%)
ASA, yes, *n* (%)	57 (88%)	26 (84%)	31 (91%)
Anticoagulant [a], yes, *n* (%)	19 (29%)	7 (23%)	12 (35%)
Standard laboratory parameters			
ESR, mm/h (after the first 60 min)	19 ± 11	19 ± 11	18 ± 12
ESR, mm/h (after the next 60 min)	42 ± 20	42 ± 19	41 ± 22
hsCRP, mg/L	1.51 (0.62–3.35)	1.73 (0.65–3.40)	1.43 (0.59–3.17)
IL-6, pg/mL	4.22 (2.27–9.57)	4.26 (2.17–10.01)	3.83 (2.30–8.20)
GFR, mL/min/1.73 m^2	84.0 ± 23.2	82.8 ± 21.3	85.1 ± 25.1
Uric acid, mg/dL	7.3 ± 1.7	7.7 ± 1.7	7.0 ± 1.7
Proteins, g/dL	7.1 ± 0.5	7.1 ± 0.5	7.0 ± 0.5
Albumins, g/dL	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3
Total cholesterol, mg/dL	161 ± 39	160 ± 38	162 ± 40
HDL cholesterol, mg/dL	40 ± 9	40 ± 10	41 ± 9
LDL cholesterol, mg/dL	93 ± 34	92 ± 31	95 ± 37
Triglicerides, mg/dL	135 ± 58	139 ± 66	131 ± 51
Total bilirubin, mg/dL	0.86 (0.73–1.04)	0.84 (0.72–1.04)	0.93 (0.73–1.07)
Direct bilirubin, mg/dL	0.28 (0.21–0.32)	0.28 (0.21–0.35)	0.26 (0.22–0.32)
Direct bilirubin, % of total bilirubin	34 ± 12	35 ± 11	33 ± 12
AST, IU/L	29 (21–43)	29 (21–43)	27 (21–46)
ALT, IU/L	38 (24–56)	38 (18–53)	39 (25–69)
GGTP, IU/L	35 (26–60)	38 (29–60)	35 (24–60)
Haematological and iron status parameters			
RBC count, T/L	4.7 ± 0.4	4.6 ± 0.4	4.7 ± 0.4
Haemoglobin, g/dL	13.7 ± 1.4	13.4 ± 1.6	14.0 ± 1.2
Haematocrit, %	40.8 ± 3.9	39.9 ± 4.1	41.5 ± 3.7
Anaemia[b], yes, *n* (%)	16 (25%)	10 (32%)	6 (18%)
MCV, fL	87.5 ± 5.4	87.4 ± 5.8	87.6 ± 5.2
MCV <80 fL, *n* (%)	5 (8%)	2 (6%)	3 (9%)
MCH, pg	29.4 ± 2.1	29.3 ± 2.5	29.5 ± 1.7
MCH <26 pg, *n* (%)	3 (5%)	2 (6%)	1 (3%)
MCHC, g/dL	33.6 ± 1.1	33.5 ± 1.2	33.7 ± 1.0
MCHC <32 g/dL, *n* (%)	3 (5%)	3 (10%)	0 (0%)
RDW, %	13.4 ± 1.1	13.5 ± 1.1	13.4 ± 1.1
RDW >15%, *n* (%)	5 (8%)	3 (10%)	2 (6%)
Reticulocyte count, G/L	59.9 ± 17.8	61.7 ± 18.6	58.2 ± 17.0
Reticulocyte count, % of RBC count	1.3 ± 0.4	1.4 ± 0.4	1.2 ± 0.4
CHR, pg	31.1 ± 1.9	30.7 ± 2.3	31.5 ± 1.5
CHR <28 pg, *n* (%)	4 (6%)	2 (6%)	2 (6%)
WBC count, G/L	7.2 ± 1.9	7.0 ± 1.9	7.3 ± 2.0
Neutrophile count, G/L	4.0 ± 1.3	4.2 ± 1.4	3.9 ± 1.2
Lymphocyte count, G/L	2.2 ± 0.9	2.0 ± 0.8	2.3 ± 0.9
Monocyte count, G/L	0.6 ± 0.2	0.5 ± 0.2	0.6 ± 0.2
Platelet count, G/L	220 ± 57	215 ± 55	225 ± 60
MPV, fL	9.4 ± 1.2	9.3 ± 1.0	9.5 ± 1.4
PDW, %	56 ± 6	55 ± 7	56 ± 6
Ferritin, μg/L	157 (82–276)	112 (53–270)	172 (122–282)
Iron, μg/dL	111 ± 40	99 ± 42	122 ± 34 *
Tsat, %	39 ± 15	33 ± 15	44 ± 12 **
STfR, mg/L	1.26 (1.10–1.42)	1.42 (1.26–1.70)	1.14 (0.93–1.24) ***
Hepcidin, ng/mL	98.3 (46.4–175.2)	98.5 (67.1–182.3)	91.6 (44.3–158.2)
Haemojuvelin, ng/mL	109.8 (48.0–180.5)	113.8 (44.7–166.1)	87.3 (48.4–212.1)