International Journal of Cardiology 195 (2015) 143–148

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Iron deficiency: Prevalence and relation to cardiovascular biomarkers in heart failure outpatients

Morten Schou [a,*], Helle Bosselmann [b], Freja Gaborit [a], Kasper Iversen [a], Jens P. Goetze [c], Georg Soletomas [d], Jon Rasmussen [e], Caroline Kistorp [e], Lars Kober [f], Finn Gustafsson [f], Niels Tonder [b]

[a] Department of Cardiology, Herlev University Hospital, DK-2730 Herlev, Denmark
[b] Department of Internal Medicine KNEA, North Zealand University Hospital, DK-3400 Hillerod, Denmark
[c] Department of Clinical Biochemistry, Rigshospitalet, DK-2100 Copenhagen, Denmark
[d] Department of Clinical Biochemistry, North Zealand University Hospital, DK-3400 Hillerod, Denmark
[e] Department of Endocrinology, Herlev University Hospital, DK-2730 Herlev, Denmark
[f] Department of Cardiology, Rigshospitalet, DK-2100 Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 26 February 2015
Received in revised form 7 May 2015
Accepted 17 May 2015
Available online 19 May 2015

Keywords:
Heart failure
Iron deficiency
Cardiac biomarkers
Inflammation
Heart failure clinic

ABSTRACT

Background: Both iron deficiency (ID) and cardiovascular biomarkers are associated with a poor outcome in heart failure (HF). The relationship between different cardiovascular biomarkers and ID is unknown, and the true prevalence of ID in an outpatient HF clinic is probably overlooked.
Objectives: To identify the prevalence of ID in a HF clinic and evaluate whether ID is associated with increased plasma concentrations of different cardiovascular biomarkers that carry a poor prognosis.
Methods: We prospectively included 149 patients with systolic HF referred to an outpatients HF clinic. ID was defined as ferritin < 100 μg/L or ferritin 100–300 μg/L and Tranferin-saturation < 0.20. Five different cardiovascular biomarkers were analyzed on frozen plasma.
Results: The patients had a median age of 70 (Interquartile range: 64–75) years, 25% were females, 29% were in functional class III–IV and LVEF was 32 (27–39) %. The prevalence of ID was 45% (95%-confidence interval (CI): 37–53%). In multivariate analyses, ID was not associated with plasma concentrations of troponin I, NT-proBNP, MR-proANP, chromogranin A or copeptin ($P > 0.05$ for all) but with plasma concentrations of hs-CRP (odds ratio: 2.03, 95%-CI: 1.02–4.02, $P = 0.043$).
Conclusion: ID is frequent in an outpatient HF clinic. ID is not associated with cardiovascular biomarkers after adjustment for traditional confounders. Inflammation, but not neurohormonal activation is associated with ID in systolic HF. Further studies are needed to understand iron metabolism in elderly HF patients

1. Introduction

Iron deficiency (ID) independent of anemia may be an overlooked condition in patients with chronic heart failure (HF) [1]. Observational studies have suggested an ID prevalence of 30–50% [1], that it is associated with an increased mortality risk [2,3] and that it is associated to reduced exercise tolerance [4]. Randomized clinical trials have suggested that correction of ID may improve symptoms and quality of life [5,6]. Whether correction of ID prevents progression of HF, e.g. time to death from pump failure or sudden cardiac death is at present unknown and more knowledge about ID in HF is needed [1].

The prevalence of ID of 30–50% has been reported from small studies [1] and the largest study is a pooled analysis of patients recruited from outpatient HF clinics, patients referred to tertiary centers and patients with acute decompensated HF [7]. The prevalence of ID in older patients with comorbidity referred to a traditional European HF clinic is largely unknown [1]. Previous studies have suggested an association between ID and plasma concentrations of NT-proBNP and high-sensitive (hs)-CRP [2,7], but it is unknown whether ID is associated with other prognostic cardiovascular biomarkers like high-sensitive troponin I (myocyte injury) and copeptin (vasopressin activity).

In patients referred to an outpatient HF clinic we evaluated the prevalence of ID and tested the hypotheses that ID is associated with increased plasma concentrations of hs-CRP, troponin I and cardiovascular biomarkers reflecting neurohormonal activity. Explorative analyses on the association between ID, ID induced anemia and mortality risk were also made.

2. Methods

Patients ($n = 149$) were included prospectively from our HF clinic at North Zealand Hospital, University of Copenhagen, Denmark, as

* Corresponding author at: Department of Cardiology S, Herlev University Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.
E-mail address: m.schou@dadlnet.dk (M. Schou).

http://dx.doi.org/10.1016/j.ijcard.2015.05.096
0167-5273/

previously described [8]. Patients with known systolic HF (left ventricular ejection fraction (LVEF) <45% by echocardiography) can be referred to the clinic. At the baseline visit, all patients were examined by a physician and the following information was obtained: medical history, medication, New York Heart Association (NYHA) classification based on patient information, physical examination including measurements of height and weight, blood pressure and heart rate at rest, X-ray of heart and lungs and electrocardiogram. Data were entered real time in a clinical database. Blood was drawn and plasma was frozen at −80 °C immediately. Informed consent was obtained according to Helsinki Declaration II and the protocol was approved by The Ethical Committee of Copenhagen (H-1-2010-074).

3. Analysis

After a >8-hour overnight fast and 15-minute rest, venous blood samples were obtained and directly analyzed for hematological tests including complete iron status, Hemoglobin A1c, TSH, Vitamin D, liver function, creatinine, sodium and potassium. For the storage of plasma for later analysis, samples were collected in EDTA (ethylenediamine tetracetic acid) vials and centrifuged at 4 °C (3000 rpm in 10 min) and stored as frozen plasma at −80 °C in aliquots until final analysis. Plasma concentrations of NT-proBNP, troponin I and hs-CRP were measured on the Dimension Vista®1500 from Siemens Medical Solutions Diagnostics using the LOCI®-technology (Luminescent Oxygen Channeling Assay) according to the manufacturer's procedures. Plasma concentrations of copeptin were measured on the Kryptor Compact platform (BRAHMS) assay and validation has been reported previously [9]. Total proANP was measured with a processing-independent radioimmunoassay, which quantitates the total sum of unprocessed and processed N-terminal proANP fragments [10]. Plasma concentrations of chromogranin A were measured with an immunoassay as previously described [11]. Renal function was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), incorporating age, race, sex, and plasma creatinine concentrations [12].

4. End point: all cause mortality

The primary end-point was death from all causes obtained from the Danish Central Personal Registry, where all deaths in Denmark are registered within 2 weeks. Thus, in (April 2015) the central registry provided 3.1 years (median) of follow-up (range: 0.3 to 5.3 years) for patients included in the current analyses. One patient emigrated and was censored at time of emigration (after 128 days), one patient had reported a wrong civilization number, but no other patients were lost to follow-up.

5. Statistics

ID was defined as: ferritin < 100 mg/L, or 100–300 mg/L with transferrin saturation < 20%. Data are presented as percentages for dichotomous variables and medians and 95% percentiles for continuous variables. Groups were compared with Chi^2-test for discrete variables and t-tests (parametric) and Mann Whitney U-tests (nonparametric) for continuous variables, as appropriate. Univariate and multivariate logistic regression models were performed for the relation between ID and each cardiovascular biomarker, with the cardiovascular biomarker as the response variable (+/− median) in separate models. Explanatory variables (covariates) were chosen from available established confounders: eGFR, LVEF, diabetes, ischemic heart disease, atrial fibrillation, body mass index, age and gender. Data quality of covariates included in the statistical models was >90%. Complete case analyses were performed. If mean substitution was performed it did not change the parameter estimate significantly for ID. The associations between ID and DM/Hemoglobin A1c were evaluated in additional logistic and linear regression models adjusted for age, sex, body-mass-index and hs-CRP. The associations between ID or ID induced anemia and mortality were examined using Cox proportional hazard model. Survival curves were generated by means of Kaplan–Meier estimates, and differences in survival were compared using log-rank test. Cox Proportional multivariate hazard models were fitted with the use of age, sex and NT-proBNP. The associations between ID or ID induced anemia and mortality risk were evaluated by a univariate analysis (model 1), after adjustment for age and sex (model 2) and after adjustment for age, sex and NT-proBNP (model 3). The assumptions underlying the Cox proportional-hazard model (proportional hazard, lack of interaction, and linearity of continuous variables) were tested and found to be valid. A P-value < 0.05 was considered significant (two-sided). Analyses were performed using Statistical Analysis Software (SAS 9.1, Cary, NC, USA).

6. Results

In the period from January 2011–November 2012 N = 230 patients with systolic HF were referred to the HF clinic and N = 149 accepted a blood test for a biobank. Patient characteristics according to ID are presented in Table 1. Patients with ID were more frequently female (P = 0.007), had more frequent diabetes (P = 0.007), were more symptomatic according to functional class (P = 0.030) and received more often a mineralocorticoid receptor antagonist (P = 0.029). ID was present in 67 patients equal to a prevalence of 45 (95-% confidence interval: 45–53) % and 14% had ID induced anemia (Fig. 1). In Table 1 it is also shown that patients with ID had smaller mean corpuscular volume (MCV) (P = 0.012) and lower mean corpuscular hemoglobin concentrations (MCHC) (P < 0.001). Leucocyte (P = 0.015) and platelet (P = 0.038) counts were also increased in patients with ID.

In Table 2 are the associations between ID and cardiovascular biomarkers presented. It should be noted that ID was not associated with any of these biomarkers (P > 0.05 for all), but in Fig. 2 it is shown that ID was associated with increased plasma concentrations of hs-CRP (P = 0.034) in a multivariate analysis.

ID was also associated with higher levels of Hemoglobin A1c (Table 1) and this association remained significant in a multivariate linear regression model with Hemoglobin A1c as response variable and ID as explanatory variable adjusted for age, sex, body-mass-index and hs-CRP (β_{ID} = 0.382, 95%-confidence interval: 0.076–0.689, P = 0.015). The association between ID and known diabetes also remained significant in a multivariate logistic regression model adjusted as above (odds $ratio_{ID}$: 2.92, 95%-confidence interval: 1.18–7.25, P = 0.021).

Kaplan–Meier plots showing mortality rates according to +/− ID (Fig. 3a) (P = 0.501) and according to no ID, ID and ID induced anemia (Fig. 3b) (P = 0.045). In the follow-up period 39 patients died. Univariate and multivariable Cox proportional hazard models are presented in Table 3. ID was not associated with an increased mortality risk in any analyses. This was, however, the case for ID induced anemia in univariate (P = 0.050) and multivariate analyses adjusted for age and sex (P = 0.027), but not after additional adjustment for NT-proBNP (P = 0.108).

7. Discussion

The main findings of the present study are: I) the observed prevalence of ID is 45% in systolic HF patient referred to an outpatient HF clinic, and II) ID is not associated with cardiovascular biomarkers reflecting neurohormonal activation, but is associated with hs-CRP. Finally, the observed association between iron metabolism and glycemic status in HF warrant further investigations. In additional explorative analyses on the association between ID and mortality risk, we did not observe an independent association in these elderly patients with systolic HF.

7.1. Prevalence of ID

We observed a high prevalence of ID in relatively older patients referred to an outpatient HF clinic. Our data do, therefore, support that