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Iron deficiency and health-related quality of life in chronic heart failure: Results from a multicenter European study

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ABSTRACT

Patients affected by chronic heart failure (CHF) present significant impairment of health-related quality of life (HRQoL). Iron deficiency (ID) is a common comorbidity in CHF with negative impact in prognosis and functional capacity. The role of iron in energy metabolism could be the link between ID and HRQoL. There is little information about the role of ID on HRQoL in patients with CHF. We evaluate the impact of ID on HRQoL and the interaction with the anaemia status, iron status, clinical baseline information and HRQoL, measured with the Minnesota Living with Heart Failure questionnaire (MLHFQ) was obtained at baseline in an international cohort of 1278 patients with CHF. Baseline characteristics were median age 68 ± 12, 882 (69%) were males, ejection fraction was 38% ± 15 and NYHA class was I/II/III/IV (156/247/487/66). ID (defined as ferritin level < 100 μg/L or serum ferritin 100–299 μg/L in combination with a TSAT < 20%) was present in 741 patients (58%). 449 (35%) patients were anaemic. Unadjusted global scores of MLHFQ (where higher scores reflect worse HRQoL) were worse in ID and anaemic patients (ID+: 42 ± 25 vs. ID−: 37 ± 25; p-value = 0.001 and A+: 46 ± 25 vs. A−: 37 ± 25; p-value < 0.001). The combined influence of ID and anaemia was explored with different multivariable regression models, showing that ID but not anaemia was associated with impaired HRQoL. ID has a negative impact on HRQoL in CHF patients, and this is independent of the presence of anaemia.

1. Introduction

In addition to the negative impact of chronic heart failure (CHF) in their prognosis, patients affected by this syndrome report a substantial impairment of their health-related quality of life (HRQoL) compared to normal populations and to patients with other chronic conditions [1]. The current profile of "real-world" heart failure patients (advanced age, the presence of multiple comorbidities) and a certain ceiling effect in the improvement of mortality and morbidity with current treatments [2] have generated great interest in emerging comorbidities and HRQoL as potential therapeutic targets [3–6].

Health-related quality of life can therefore be seen as a patient-centred outcome that shows association with prognostic and other markers of severity in patients with CHF [7]. Due to its multidimensional nature, it enables the health care provider and the researcher to obtain additional information on the impact of the disease from the patients' perspective, information that could not be fully obtained by other conventional methods usually used to diagnose and/or monitor the course of this syndrome [8]. Thus, from the point of view of patients and caregivers, HRQoL can be viewed per se as a patient-centred measure of efficacy better representing their interests and preferences [9,10]. In this respect, a substantial proportion of patients with CHF would trade better HRQoL for survival at some point in their evolution [11]. In consequence, HRQoL has become an extremely important subject to build the foundations of the new concept person-centred care [4,5].

There is a growing interest in exploring the determinants of HRQoL particularly for comorbidities that would be potentially treatable translating these interventions into improvements [5]. In recently published studies in the field of CHF, iron deficiency has emerged as a common

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comorbidity with a negative impact on both prognosis and functional capacity [12–15]. Furthermore, there is evidence that the correction of iron deficiency with intravenous iron can improve symptoms, functional capacity and HRQoL in these patients, regardless of the presence or absence of anaemia [6,16–19]. These findings suggest that iron deficiency might be a key modifiable determining factor of functional limitation and impaired HRQoL. The crucial role that iron plays in energy metabolism in cardiac and skeletal muscles could give support to the rationale of the hypothesis linking iron with HRQoL and symptoms in CHF [16,20].

Despite this, information [21] about the role of iron deficiency on HRQoL in patients with CHF is scarce. To elucidate this question, we conducted a multicentre international descriptive cross-sectional study with 1278 patients with CHF to evaluate the impact of iron deficiency on HRQoL and consider whether the potential influence of iron deficiency is modulated by the anaemic status of patients.

2. Methods

2.1. Component studies

The studied cohort comprised 1278 patients with chronic HF and reduced or preserved left ventricular ejection fraction (LVEF) from 4 different cohorts recruited in Poland, Spain and the Netherlands. Preserved left ventricular systolic function was defined as LVEF > 45%, as proposed in previous studies [22]. The inclusion and exclusion criteria per participating study cohort have been published previously by our group [14]. For the evaluation of the influence of ID and/or anaemia on HRQoL, only patients with available HRQoL, iron indices and anemia status evaluation were included. The Spanish cohort consisted in 714 chronic HF patients with reduced or preserved ejection fraction in stable condition referred to the outpatient heart failure unit [21]. The Polish cohort comprised 279 patients with chronic HF and reduced LVEF in stable condition who were attending outpatient clinics or admitted electively to one tertiary referral cardiology centre [12,13]. Finally, two Dutch patient cohorts comprising 285 stable chronic HF patients with reduced or preserved LVEF were included in the present analysis [23,24]. All study protocols were approved by local ethics committees and all patients gave written informed consent for the present study. A proportion of patients had been enrolled in other studies, for which they had given consent before. These patients were consented separately again. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Pooled methodology

This methodology has been published previously by our group [14]. The pooled data in the present study were all assessed at a patient level. All 4 cohorts were chosen for the present analysis because they had comparable clinical information available. This included standard demographic information, New York Heart Association (NYHA) functional classification, current medical therapy, physical examination, results of plasma and serum chemistry tests and LVEF, assessed via echocardiography or radionuclide ventriculography. None of the patients received blood transfusions, erythropoietin therapy or intravenous iron therapy at the time of inclusion.

2.3. Iron status and other laboratory measurements

Peripheral venous blood samples were collected from all patients. Hematologic indices were assessed from fresh venous blood using EDTA. After centrifugation, the remainder was frozen and stored prior to analysis. Anaemia was defined as a haemoglobin level < 12 g/dL in women and <13 g/dL in men [25].

The following blood biomarkers reflecting iron status were measured: ferritin (μg/L), serum iron (μg/L), total iron binding capacity (μg/L) and transferrin (mg/dL). Transferrin saturation was reported as a ratio of 0.7217 × serum iron and transferrin, multiplied by 100 [26]. When transferrin was not available, transferrin saturation (TSAT) was reported as a ratio of serum iron (μg/L) and TIBC (μg/L) multiplied by 100. There was a strong correlation between both TSAT measurements ($R^2 = 0.89$, $p < 0.001$). ID was defined as a ferritin level < 100 μg/L or serum ferritin 100–299 μg/L in combination with a TSAT < 20%. Similar definitions of ID have been used in recent observational and intervention trials in chronic HF [6,12,13]. Additional markers of iron status were also measured: mean corpuscular haemoglobin (MCH) and red cell distribution width (RDW). MCH is the content of haemoglobin in the mature red cells and is a measure of iron-restricted erythropoiesis [27]. RDW is a measurement of the size of variation of erythrocyte volume [28,29]. It is determined automatically by most haematology analysers and calculated by dividing the standard deviation of erythrocyte volume [mean corpuscular volume (MCV)] by the mean of MCV [28]. Normal reference values for RDW are considered to be between 11% and 14%, and a greater RDW indicates variations in erythrocyte size and composition, which is defined as anisocytosis. A close relationship between RDW and circulating iron parameters has been found in recent studies and consequently this new parameter has been postulated as a promising measure of iron status [29,30]. Concentrations of N-terminal pro-brain-type natriuretic peptide (NT-proBNP, pg/mL) were measured using an immunoassay based on electrochemiluminescence on the Elecsys System (Roche Diagnostics). Renal function was assessed by using the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate the glomerular filtration rate (eGFR, mL/min/1.73 m^2). Serum concentrations of high-sensitive C-reactive protein (hs-CRP, mg/L) or C-reactive protein were assessed at each institution using standard methods. In 185 patients from Holland both measures were available and showed a highly significant correlation ($r = 0.950$; p-value < 0.001). In univariate and multivariate analysis the standardized value of Hs-CRP or CRP per centre was used.

2.4. HRQoL evaluation

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) [31] is a self-administered questionnaire consisting of 21 individual items. In addition, it provides an overall measure of health (global summary score) and summary scores of the physical and emotional dimensions of health, based on 8 and 5 items, respectively. The was self-administered by all patients at inclusion in the study [1,2]. For each item in the MLHFQ, responses were scored from 0 (no impact on HRQoL) to 5 (maximum impact on HRQoL). Summary scores were obtained by summing responses to each of the items, giving a summary score of 0–105. For the present study, summary scores of the physical and emotional dimensions were not available for all patients and thus, are not reported.

2.5. Statistical analyses

Data are expressed as means ± SD (standard deviation) when normally distributed or as medians with interquartile range when non-normally distributed. Data presented from general linear models are expressed as marginal means ± SE (standard error). Inter-group differences were tested using Student t test, or Mann–Whitney U-test when appropriate. For further analyses, logarithmic transformation was performed to achieve a normal distribution for skewed variables (NT-proBNP, ferritin, TSAT and CRP). Categorical variables were expressed as numbers and percentages. The inter-group differences were tested using the Pearson Chi^2 tests.

Univariate linear regression analyses were undertaken to explore the influence of demographic and clinical variables, including measures of iron and anaemia status, on HRQoL. To evaluate the effect of ID and anaemia together on HRQoL, 5 multivariable linear regression models were constructed. The first model included ID according to the FAIR-HF definition [6] and anaemia, and the second model included haemoglobin as a continuous variable instead of anaemia. Models 3, 4 and 5 included TSAT, RDW and MCH respectively to express iron status and Hb, all of them as continuous variables. Multivariate models were adjusted for all covariates that showed association with the HRQoL score ($p < 0.10$) in univariate analyses, as well as age, gender and LVEF.

To explore the influence on HRQoL of the combined state of ID and anaemia, a multivariable binary regression model was constructed using worse HRQoL as a dependent variable (defined as MLHFQ scores in the upper tertile). This model was adjusted for the variables associated with the dependent variable in univariate analyses.

General linear modelling adjusted for univariate associated variables was used to explore several aspects of the relationship between iron and anaemia status and HRQoL, particularly to evaluate the distribution of concentrations of TSAT or haemoglobin according to HRQoL scores (divided in quartiles).

Finally, to explore interactions between iron status and haemoglobin (divided in 5 categories) and their effects on HRQoL, 3 different general linear models were developed. The first, included ID (ferritin level < 100 μg/L or serum ferritin 100–299 μg/L in combination with a TSAT < 20%), the second included TSAT divided in 3 categories and the third included RDW > 15% (when MCV was ≤ 100 fL) as an indicator of iron-deficient anisocytosis. All models included haemoglobin divided in 5 categories, to analyse the interplay in terms of HRQoL between this variable and iron status with a special interest in the normal-to-low ranges of haemoglobin. All 3 models were adjusted for age, gender, centre as well as for covariates associated with the level of severity of CHF (including systolic blood pressure, diabetes, aetiology of HF, CRP, NT-proBNP, LVEF, left ventricular diastolic dimensions, presence of atrial fibrillation, body mass index, estimated glomerular filtration rate and NYHA functional class). p-Values <0.05 were considered statistically significant. SPSS version 18.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 1278 patients included into the study are shown in Table 1. ID was present in 741 (58%) patients. Up to 449 patients (35%) were anaemic. Distribution of patients according to the presence (A^+) or absence (A^-) of anaemia and the presence (ID^+) or absence (ID^-) of ID was: A^-/ID^- in 396 (31%), A^+/ID^- in 141 (11%), A^-/ID^+ in 433 (34%) and A^+/ID^+ in 308 (24%). Anaemic patients were more often iron-deficient compared to non-anaemic patients (69% vs 52% respectively; p < 0.001). Patients with ID were older, had worse NYHA functional class, had higher NT-proBNP levels, were more often anaemic and had higher prevalence of diabetes and renal dysfunction. As expected, levels of haemoglobin and biomarkers of iron status were