Pulmoner Arteryel Sistolik Basınç ve Sağ Kalp Yetersizliği Semptomları: Kalp Yetersizliği Hastalarında Demir Eksikliğinin Demir Eksikliği Anemisine İlerlemesinde Bir Belirteç

Pulmonary Artery Systolic Pressure and Right Sided Heart Failure Symptoms: a Predictor for Progression of Iron Deficiency to Iron Deficiency Anemia in Heart Failure Patients

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ÖZ

GİRİŞ ve AMAÇ: *Kalp yetersizliği (KY) hastalarında sık karşılaşılan demir eksikliği (DE) ve demir eksikliği anemisi (DEA) artmış mortalite ve morbidite ile ilişkili komorbiditelerdir. KY hastalarında demir eksikliği iyi bilinen hastalıklardan olmasına rağmen ülkemizde KY hastalarında DE ve DEA ile ilgili yeterli epidemiyolojik çalışma bulunmamaktadır. Bu çalışmanın ilk amacı KY hastalarında DE ve DEA anemisi prevalansını değerlendirmek; ikinci amacı ise, KY hastalarında DE'nin DEA'ne ilerlemesini hızlandıran faktörleri saptamaktır.*

YÖNTEM ve GEREÇLER: *288 kalp yetersizliği hastasında serum demir, ferritin, total demir bağlama kapasitesi (TDBK) ve transferrin saturasyonu (TS) çalışıldı. DE serum ferritin<100µg/L (mutlak DE) veya ferritin 100-299 µg/L arasında ve TDBK<20% (fonksiyonel DE) olarak tanımlandı. Anemi erkeklerde haemoglobin <13g/dl ve kadınlarda <12g/dl olarak tanımlandı. KY hastalarında DE anemisinin klinik belirleyicileri tek değişkenli ve çok değişkenli lojistik regresyon modelleri kullanılarak değerlendirildi.*

BULGULAR: *288 KY hastası değerlendirildi. Bu hastalardan 239 tanesinde (83.3%) DE saptandı. 49 tanesinde ise (16.7%) DE yoktu. Demir eksikliği prevalansı 83.3%, demir eksikliği anemisi prevalansı ise 44% (127/288) idi. Çoklu regresyon analizinde pulmoner arteryel sistolik basınç (PASB), sağ kalp yetersizliği semptomları, eGFR ve sedimantasyon DEA ile bağımsız olarak korale idi (P=0.027; P=0.033; P=0.086; P=0.001 sırasıyla).*

TARTIŞMA ve SONUÇ: *PASB ve sağ kalp yetersizliği semptomları DEA için bağımsız bir belirteç olarak dikkat çekmektedir.*

Anahtar Kelimeler: *Demir Eksikliği, Demir Eksikliği Anemisi, Kalp yetersizliği*

ABSTRACT

INTRODUCTION: *Iron deficiency (ID) and iron deficiency anemia (IDA) are common comorbidity in heart failure (HF). Although ID is well-known subject in HF patients, there are not enough epidemiological studies examining the prevalence of ID and IDA in HF patients in our country. The aim of this study is to evaluate the prevelance of ID and IDA in Turkey and to detect a marker for progression of ID to IDA in HF patients.*

METHODS: *ID was described as serum ferritin<100µg/L (absolute ID) or ferritin level 100-299 µg/L with TSAT<20% (functional ID).Anemia was described as a hemoglobin level<13g/dl in males and <12g/dl in females. Clinical determinants of IDA in patients with HF were established using univariate and multivariable logistic regression models.*

RESULTS: *We examined 288HF patients.239 (83.3%) were HF patients with ID and 49 (16.7%) were HF patients without ID. ID prevalence was 83.3% and IDA prevalence was 44% (127/288) among all HF patients in our study. Multivariate regression analysis; pulmonary artery systolic pressure (PASP), right heart failure (RHF) symptoms, eGFR and sedimentation appeared as independently correlate with the HF patients who had IDA (P=0.027; P=0.033; P=0.086; P=0.001 respectively).*

DISCUSSION AND CONCLUSION: *Remarkably, PASP and RHF symptoms were independent predictor for IDA. These parameters may be an early marker for progression of iron deficiency to iron deficiency anemia in HF patients.*

Keywords: *Iron Deficiency, Iron Deficiency Anemia, Heart Failure*

INTRODUCTION

Despite the major advances in heart failure treatment, high mortality rates, poor functional capacity and limited improvement in symptoms remain an important health problem in a large group of patients (1-3). Further treatment goals are needed to reduce this mortality and morbidity burden. Iron deficiency (ID) and anemia is a frequently present comorbidity in patients with heart failure (HF).

Iron is an crucial nutritional element that functions as a cofactor in the functioning of numerous enzymes and proteins in the human body. It also plays a role in mitochondrial reactions, regulation of nitric-oxide in vascular smooth muscle, cellular redox regulation, transcription, immunochemical events and neurotransmission (4-6).Iron metabolism is especially important in cells that are working with high energy, such as heart muscle. Total body iron stores are regulated only by iron absorption, which is controlled by hepcidine, the hepatocyte-derived peptide hormon released from the liver (7). The release of heptidine, which is induced by inflammation in functional ID, results in a reduce in iron absorption and inhibition of transfer of iron from macrophages to erythrocyte precursors (8)

A serum ferritin <30 ng/ml is defined as absolute ID in general population indicating a significant iron depletion in bone marrow. As ferritin is an acute phase reactant, this cut off value doesn't appear to be applicable in chronic inflammatory diseases such as chronic HF (9-10). Therefore, absolute ID is described as a ferritin level <100mg/L in these conditions. Age-related nutritional deficiencies, impaired gastrointestinal absorption due to chronic blood loss and intestinal edema associated with co-morbidities may lead to this condition in patients with HF. Liver congestion plays a role in the improving absolute ID by inducing inflammation in hepatocytes and resulting in decreased iron content. Functional ID described as a ferritin level between 100-300mg/dL and a transferrin saturation <20% is associated with the inability to adequately meet the iron demand of the tissues in spite of normal body deposits. There is a

deficit in iron mobilization suggesting an increase in the production of hepcidine secondary to increased inflammation and decreased iron absorption (11-14). A transferrin saturation less than 20% is the best measure for the diagnosis of functional ID. It reflects the amount of circulatory iron that can be utilized for peripheral metabolism. Transferrin is a negative acute phase reactant that decreases with inflammation (12) and decreased hepatocytic secretion of transferrin causes decreased serum iron values (13).

Anemia, defined as a haemoglobin <13g/dl in males and <12g/dl in females according to World Health Organization(14), is common in patients with HF, and is often associated with ID. Anemia and ID either with or without the presence of anemia have been associated with increased cardiovascular mortality, making a target for therapy (15).

Prevalence and outcome of ID in HF patients have been investigated in abundant number of studies previously. Nevertheless, our knowledge is limited to the prevalence in our country and we do not have enough data about the predictors of progression of ID to ID anemia. We tried to clarify them in our study.

MATERIAL AND METHODS

Study design and population

Patients with heart failure with reduced and mid-range ejection fraction were consequently included in this study. Exclusion criteria were left ventricle EF over 45%, acute myocarditis, restrictive and hypertrophic cardiomyopathy, active infection, dialysis, pregnancy, malignancy, connective tissue diseases autoimmune and inflammatory diseases, prior myocardial infarction within the last 3 months.

All participants underwent clinical examination, and conventional transthoracic echocardiography (Vivid 7, GE Ving Med Ultrasound AS; Norway, Horten). Measurements of left ventricle (LV), right ventricle (RV) and the left atrium (LA) were obtained from the apical four chamber and parasternal-long axis views, in accordance with the

standard criteria. LVEF was calculated using the modified Simpson method in the apical two chamber and four chamber views. For calculate pulmonary artery systolic pressure (PASP); the transtricuspid valve gradient was calculated by the modified Bernoulli formula where the maximal velocity of the tricuspid regurgitant jet. Right atrium pressure was calculated by the respiratory variation in the inferior vena cava diameter and was classified as 5-10 and 15 mmHg. Right ventricular systolic pressure was calculated by adding the tricuspid gradient to right atrium pressure level.

Right sided HF was defined as the presence of the symptoms (ankle swelling) or specific signs (ascites, abdominojugular reflux or jugular venous distention) of right HF.

Fasting blood samples were drawn for the determination of hemostatic and biochemical values. Ferritin levels were measured with Beckman Coulter, Access Immunassay Systems. Iron was measured with Cobas C 702 Systems. Creatinine and urea were measured by standard methods and estimated glomerular filtration rate(eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

The study was approved by local institutional Ethics Committee.

Statistical analysis

The SPSS 13.0 (SPSS Inc. an IBM company;Chicago,USA) package was used for statistical analyses. Normality tests were performed for all variables using Kolmogorov Smirnov test. Normally distributed variables are presented as mean ± SD, and abnormally distributed variables are given as median. Categorical data are presented as percentages and numbers. Normally distributed continuous variables were analyzed with the 2-tailed Student's-t test, and not normally distributed variables were analyzed with the MannWhitney-U test. Categorical data and proportions were evaluated using the Chi-square or Fisher exact test where appropriate. Pearson and Spearman tests used for correlation analysis. The Pearson correlation was used to analyze the linear

relationship between two continuous variables. The Spearman correlation was performed to evaluate to the relationship between two continuous or ordinal variables. Clinical determinants of HF patients with ID anemia were established using univariate and multivari¬able logistic regression models. The following vari¬ables were included in the analyses: eGFR, age, right heart failure symptoms, EF, NT-proBNP, CRP, right ventricle diameter, PASP, sedimentation, direct bilirubin, total bilirubin, alanine amino-transferase, aspartate aminotransferase, indirect bilirubin. A p value <0.05 was accepted statistically significant.

RESULTS

We examined 288 heart failure patients. 239 of them (83.3%) were HF patients with ID and 49 of them (16.7%) were HF patients without ID. Absolute ID was 217 (91%) patients and functional ID was 22 (9%) patients.

ID anemia prevalence was 44% (127/288) among all HF patients in our study. Also, the ID anemia prevelance was 53% (127/239) among HF patients with ID.

The study group consisted of 127 HF patients with ID anemia (Group 1) and 112 HF patients with ID who did not have anemia (Group 2). Baseline characteristics of the study are presented in **Table 1.** HF patients with ID anemia were older than the HF patients with ID who did not have anemia (70.8±11.3 vs 67.6±12; P=0.029) and more male in the ID anemia group (80/47 (63%-37%) vs 54/57 (49%-51%); P=0.026).

HF patients with ID anemia had higher NYHA class compared to the patients with ID who did not have anemia (P=0.042). HF patients with ID anemia were lower body mass index (BMI) compared to the patients with ID who did not have anemia (26.5 (24-28.9) vs 27.5 (25-31.2); P=0.023).

RHF symptoms were defined as the presence of the symptoms (ankle swelling) or specific signs (ascites, abdominojugular reflux or jugular venous distention). HF patients with ID anemia had higher RHF symptoms (78 (61.4%) vs 43 (38.7%); P<0.001)

Table 1: Baseline characteristics of iron deficiency with and without anemia in HF patients			
Characteristic	Iron deficiency anemia in HF patients (n=127)	Iron deficiency without anemia in HF patients (n=112)	P-value
Age (years)	70.8±11.3	67.6±12	0.029
Male/female	80/47 (63%-37%)	54/57 (49%-51%)	0.026
NYHA Functional Classification NYHA 1 NYHA 2 NYHA 3 NYHA 4	6 (4.7%) 45 (35.4%) 74 (58.3%) 2 (1.6%)	11 (9.9%) 52 (46.8%) 45 (40.5%) 3 (2.7%)	0.042
Body mass index (kg/m2)	26.5 (24-28.9)	27.5 (25-31.2)	0.023
Coronary Artery disease	82 (64.6%)	55 (49.5%)	0.064
Hypertension	85 (66.9%)	71 (64%)	0.637
Diabetes mellitus	50 (39.4%)	30 (27%)	0.05
Right heart failure symptoms	78 (61.4%)	43 (38.7%)	<0.001
Echocardiographic parameters			
Ejection fraction (%)	35 (25-45)	35 (25-45)	0.936
LVEDD (mm)	55.6±8.2	55.7±9.5	0.948
Left atrium diameter (mm)	44 (40-49)	45 (38-51)	0.965
Right ventricular diameter (mm)	26 (24-28.5)	25 (23-27)	0.014
sPAP (mmHg)	40 (30-50)	30 (20-45)	<0.001
Medications			
ACE-I/ARB	63 (49.6%)	63 (56.8%)	0.238
Beta- blockers	82 (64.6%)	84 (75.7%)	0.063
Spironolactone	17 (13.4%)	25 (22.5%)	0.065
Digoxin	15 (11.8%)	18 (16.2%)	0.398
Loop diuretics	86 (67.7%)	60 (54.1%)	0.031
Biochemical parameters			
NT-Pro BNP (pg/mL)	2550 (883-6190)	935 (197-2437)	<0.001
CRP (mg/dl)	1.15 (0.31-2.95)	0.5 (0.19-1.3)	0.002
Hemoglobin (g/dl)	11.07±1.28	14±1.26	<0.001
Hematocrit (%)	34.3 (31.6-36.4)	41.9 (38.6-44.5)	<0.001
MCV (Fl)	85 (79-90.1)	90 (84.3-93.5)	<0.001
WBC/mm³	7.4 (5.7-8.9)	7.2 (5.7-98.8)	0.974
Sedimentation	28 (15-45)	16 (9-23)	<0.001
eGFR (ml/min)	47 (33.8-71)	72.6 (50.3-91.2)	<0.001
Creatinine (mg/dl)	1.31 (0.94-1.84)	0.97 (0.82-1.2)	<0.001
Urea (mg/dl)	64 (42.5-96)	43 (30-56)	<0.001
Ferritin (ng/mL)	43.1 (21.8-73)	44.8 (23.5-73.6)	0.718
Transferrin saturation (%)	11.7 (7.2-15.9)	16.8 (11.1-24.7)	<0.001
Iron (mcg/dL)	39 (26-57)	58.5 (40-82.5)	<0.001
TIBC (mcg/dL)	339 (277-386)	332 (290-378)	0.8
AST (U/L)	20 (16-28)	20 (16-25)	0.022
ALT (U/L)	15.5 (12-25)	18 (13-23)	0.481
Total bilirubin (mg/dL)	0.65 (0.41-1.1)	0.7 (0.45-1)	0.917
Direct bilirubin (mg/dL)	0.2 (0.11-0.41)	0.2 (0.12-0.36)	0.711
Indirect bilirubin (mg/dL)	0.4 (0.23-0.6)	0.4 (0.3-0.64)	0.316

NYHA: New York Heart Association, TIBC: Total iron binding capacity, NT-Pro BNP :N-terminal pro B-type natriuretic peptide, CRP : C-reactive protein, PASP: Pulmonary artery systolic pressure, AST: Aspartate transaminase, ALT: Alanine transaminase, WBC: White blood cell count, LVEDD: Left ventricular end diastolic diameter, eGFR: Estimated glomerular filtration rate.

Hypertension, coronary Artery disease, diabetes mellitus were similar between the groups (P=0.064; P=0.637; P=0.05 respectively)

In echocardiographic parameters; right ventricular diameter was larger in the HF patients with ID anemia (26 (24-28.5) vs 25 (23-27); P=0.014). PASP was higher in the HF patients with ID anemia (40 (30-50) vs 30 (20-45); P=<0.001). EF, left ventricular end diastolic diameter (LVEDD) and left atrium diameter were similar between the groups (P=0.936; P=0.948; P=0.965 respectively)

In medications; HF patients with ID anemia were using more loop diuretics than the other group (P=0.031). ACE-I/ARB, spironolactone, beta blockers and digoxin usage were not statistically significant between groups (P=0.238; P=0.063; P=0.065; P=0.398; respectively).

In hematological and biochemical parameters; hemoglobin, hematocrit, MCV levels were lower in HF patients with ID anemia than the other group (P<0.001; P<0.001 and P<0.001 respectively). Ferritin levels were not statistically different between groups (P=0.718). Transferrin saturation and iron leves were lower in HF patients with ID anemia (P<0.001 and P<0.001 respectively). TIBC were not statistically different between groups (P=0.8). NT-Pro BNP levels were higher in HF patients with ID anemia (2550 (883-6190) vs 935 (197-2437); P<0.001). CRP, sedimentation were higher in HF patients with ID anemia (P=0.002 and P<0.001 respectively). WBC were not statistically different between groups (P=0.974). eGFR (ml/min) levels were lower in HF patients with ID anemia (47 (33.8-71) vs 72.6 (50.3-91.2); P=<0.001). Creatinine and urea levels were higher in the same group (P<0.001 and P<0.001 respectively). AST levels were higher in HF patients with ID anemia 20 (16-28) vs 20 (16-25); P=0.022). ALT, total bilirubin, direct bilirubin, indirect bilirubin were not statistically significant between groups (P=0.418; P=0.917; P=0.711 and P=0.316 respectively).

Significant univariate and multivariate clinical, echocardiographic, and laboratory correlates with HF patients with ID anemia are presented in Table 2. Age, eGFR, RHF symptoms, EF, NT pro-BNP, CRP, Sedimentation, PASP, right ventricle diameter and AST level were significantly correlated to ID anemia in univariate analysis.In multivariate analysis; PASP, RHF symptoms, eGFR and sedimentation appeared as independent correlates with the ID anemia in HF patients (P=0.027; P=0.033; P=0.086; P=0.001 respectively).

Table 2: Significant univariate and multivariate correlates of HF patients with iron deficiency anemia

Variables	Univariate regression coefficient (95% CI)	P-value	Multivariate regression coefficient (95% CI)	P-value
Age, years	1.024 (1.001-1.047)	0.037	0.988 (0.945-1.033)	0.592
eGFR (mL/min)	0.968 (0.956-0.979)	<0.001	0.979 (0.956-1.003)	0.086
RHF symptoms	0.406 (0.241-0.684)	0.001	0.228 (0.059-0.887)	**0.033**
EF (%)	1 (0.979-1.021-1.320)	0.990		
NT pro-BNP (pg/mL)	1.0 (1.0-1.0)	0.007	1.0 (1.0-1.0)	0.073
CRP (mg/dl)	1.034 (1.017-1.052)	0.059		
Sedimentation	1.002 (0.984-1.020)	<0.001	1.088 (1.037-1.142)	**0.001**
PASP (mmHg)	1.025 (1.007-1.043)	0.006	0.953 (0.914-0.995)	**0.027**
RV (mm)	1.092 (1.017-1.173)	0.016	1.063 (0.8951.262)	0.486
AST (U/L)	1.023 (1.001-1.046)	0.041	1.010 (0.973-1.049)	0.591

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; RHF: Right heart failure; PASP: Pulmonary artery systolic pressure, EF: Ejection Fraction, NT-Pro BNP: N-terminal pro B-type natriuretic peptide, RV: Right ventricle, , ALT: Alanine transaminase

DISCUSSION

PASP and right sided HF symptoms were independent predictor for the HF patients with ID anemia in our study.

In recent years, there has been an increasing awareness of the importance of ID in patients with HF. Prevalence of ID is high and related to geographic location, and ethnicity (2-16). Although ID is a well-known subject, there are not enough epidemiological studies examining the prevalence of ID and anemia in our country.

The prevalence of ID has been reported between 37% and 76% in previous studies (2,17-18) in HF patients. In a study involving 751 stable chronic HF patients from a multi ethnic Asian population, ID was detected in 61.4% of the patients. In an Indian study (19) involving 150 patients admitted to the hospital with clinical diagnosis of HF, the prevalence of ID was 76% with 48.7% patients having absolute ID and 27.3% patients having functional ID.

In studies conducted in Europe; the rates are mostly lower. Jankowska et al. studied 546 patients with stable systolic HF and identified 37% of them as having ID (10). In another study, 1506 HF patients with preserved or reduced LVEF were evaluated in 5 European chronic HF cohort analyses and 50% of them were found to have ID and 28% of them had anemia (2). In another study from Belgium the prevelance of ID was 56% at cardiac resynchronization therapy, while absolute ID was present in 62% of them and functional ID was 38% (20).

Patients with heart failure and EF≤40% were recruited by 11 centers in Germany and Switzerland. ID was observed in 54.7% of patients (21). A multicenter study in France evaluating iron status of 832 patients hospitalized for decompensation of chronic HF demonstrated that ID was present in 69% of men and 75% of women. ID was found in 65% patients with acute HF in Poland (22).In a separate study from Greece, ID anaemia was diagnosed by bone marrow aspiration in 73% of the patients with advanced congestive HF (23). ID was mainly absolute and common in both nonanaemic and anaemic patients(24).

As understood; Malaysian, Chinese and Indian patients with ID has higher prevalence than the European patients. However, there are not enough epidemiological studies examining the prevalence of ID in our country. The only data in the literature is an observational TAK-TIK (Turkish registry for diagnosis and treatment of acute heart failure) study. It included 558 acute HF patients and described that mean haemoglobin value is 12.4±2.1g/dl. Secondary blood analysis was not performed for the presence of anemia in this study.

However, a mean Hb level of 12.4 g/dL proposes that the prevalence might be aproximatelly 50% (25-26).

In our study; ID was 83.3% (%7,5 was fuctional, 75,8% was absolute ID) and ID anemia was 44% in all HF patients. Also, the ID anemia prevelance was 53% (127/239) among HF patients with ID. The ratios of ID, absolute ID and ID anemia were higher in our study group compared to the results of previous studies. Regional-ethnic characteristics and nutriotional habits may be responsible for relatively high proportion of ID in our study group. Another rational explanion for increased ratios in our study may be relatively higher proportion of advanced heart failure patients, as the study group was recruited from a tertiary center. However, this relatively high frequency of ID in HF patients can draw attention to detect and manage ID in Turkish population.

Inflammation is an important component of HF. Klip IT et al. found that high sensitive-CRP levels in patients with chronic HF were associated with ID (2). Jankowska et al. performed a study including 546 stable patients with chronic HF, an independent association was found between ID and high plasma CRP level (10). Schou et al. found ID was associated with hs-CRP in systolic heart failure (27). In our study CRP level was similarly higher as in other studies. Liver congestion can play a important role in the progression of absolute ID by inducing inflammation in hepatocytes and resulting in decreased iron content.

The pathogenesis of anemia in HF is complex. When ID is severe in a level that will reduce the production of erythropoiesis and hemoglobin, anemia occurs (14). Liver congestion, gastrointestinal absorption due to intestinal edema and nutritional disorders associated with them may lead to this condition in patients with HF. Intestinal congestion is associated with iron malabsorption, postprandial fullness, appetite loss and it may results from venous congestion of the bowel wall due to the right sided HF. In patients with right sided HF, iron absorption due to intestinal congestion is impaired and anemia development is accelerated. In our study, remarkably PASP and

right sided HF symptoms (the presence of at least one of the symptoms:ankle swelling or specific signs: ascites, abdominojugular reflux or jugular venous distention) were independent predictor for the HF patients with ID anemia and they can explain these reasons.

In addition Valentova M et al found that cardiac cachexia and malabsorption was associated with intestinal congestion (28). In our study; HF patients with ID anemia had lower BMI compared to the HF patients with ID who had not anemia. Our findings supported their evidence.

Clinicians might consider the PASP and right sided HF symptoms to detect the high risk patients for ID anemia in HF patients.

CONCLUSION

ID prevalence was 83.3% in our study. This rate was significantly higher than the other studies. This situation draws attention to the frequency of ID in patients with HF in Turkey, mainly in the form of absolute deficiency. Remarkably, PASP and right sided HF symptoms were independent predictor for the HF patients with ID anemia. These parameters may be an early marker of the ID patients with high risk of developing anemia.

LIMITATIONS

Our study has several limitations. This study is a single center study. As Turkey is a country with diverse dietary habits and cultures, there is a need for greater multi-centered work. If we used measurements evaluating right ventricular functions (for example TAPSE), there could be more supportive findings.

Conflict of interest: None declared.

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