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The Effects of Iron Replacement on Functional Capacity in Patients with Group 1 and Group 4 Pulmonary Hypertension

Grup 1 ve Grup 4 Pulmoner Hipertansiyon Hastalarında Demir Replasmanının Fonksiyonel Kapasite Üzerine Etkileri

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: Abnormal iron handling complicates pulmonary hypertension and causes functional limitation and poor outcomes. Although preliminary results in group 1 pulmonary hypertension patients support the use of iron replacement, whether this applies to other PH subgroups is not known.

Methods: A total of 58 patients with an established diagnosis of group 1 or 4 pulmonary hypertension, who had serum ferritin of <100 ng/mL or 100–300 ng/mL in combination with a transferrin saturation <20% and received 500–1000 mg of ferric carboxymaltose, were included in the study. The change in ferritin levels and transferrin saturation was calculated at 12- and 24-week follow-up. A six-minute walk test is undertaken at the first, 12-week, and 24-week follow-up visits.

Results: In group 1 pulmonary hypertension patients, ferritin levels increased from 14 ng/mL to 133 and 90 ng/mL at 12- and 24-week, respectively (*P* <.001 for both). In group 4 pulmonary hypertension patients, ferritin levels increased from 22.1 ng/mL to 145 and 88.9 ng/mL at 12 and 24 weeks, respectively (*P* <.001 for both). The 6-minute walk test distances were 356, 412, and 350 m in group 1 pulmonary hypertension patients and 260, 315, and 290 m in group 4 pulmonary hypertension patients. Although the difference between baseline and 12-week 6-minute walk test was significant in both groups (*P* <.001 for both), this difference was lost at 24-week.

Conclusion: Our study indicates that there is no difference in response to iron replacement in patients with group 1 and group 4 pulmonary hypertension patients, in terms of treatment success and functional status.

Keywords: Anemia, chronic thromboembolic pulmonary hypertension, ferric carboxymaltose, pulmonary arterial hypertension, pulmonary hypertension

ÖZET

Amaç: Anormal demir kullanımı pulmoner hipertansiyonu (PH) komplike hale getirir, fonksiyonel kısıtlılığa ve kötü sonlanımlara neden olur. Grup 1 PH hastalarındaki ön sonuçlar demir replasmanının kullanımını desteklese de bunun diğer PH alt grupları için geçerli olup olmadığı bilinmemektedir. Bu çalışmada grup 1 ve grup 4 PH hastalarında demir replasmanına yanıtta tedavi başarısı ve fonksiyonel durum açısından farklılık olup olmadığını araştırmayı amaçladık.

Yöntemler: Serum ferritini <100 ng/mL veya 100 ila 300 ng/mL ve transferrin satürasyonu (TSAT) <%20 olan ve 500–1000 mg ferrik karboksimaltoz (FCM) alan, grup 1 veya 4 PH tanısı konmuş toplam 58 hasta çalışmaya dahil edildi. Ferritin seviyelerindeki ve TSAT'taki değişiklik, 12 ve 24 haftalık takipte ölçüldü. İlk, 12 haftalık ve 24 haftalık takip ziyaretlerinde altı dakikalık yürüme testi (6DYT) yapıldı.

Bulgular: Grup 1 PH hastalarında, ferritin seviyeleri 14 ng/mL'den 12. ve 24. haftalarda 133 ve 90 ng/mL'ye yükseldi (her ikisi için de *P* < ,001). Grup 4 PH hastalarında, ferritin seviyeleri 12. ve 24. haftalarda sırasıyla 22,1 ng/mL'den 145 ve 88,9 ng/mL'e yükseldi (her ikisi için *P* < ,001). 6DYT mesafeleri grup 1 PH hastalarında 356, 412 ve 350 m, grup 4 PH hastalarında 260, 315 ve 290 m idi. Başlangıç ve 12 haftalık 6DYT arasındaki fark her iki grupta da anlamlı olmasına rağmen (her ikisi için *P* < ,001) bu fark 24 haftada kaybolmuştur.

Sonuç: Çalışmamız grup 1 ve grup 4 PH hastalarında demir replasmanına yanıtta tedavi başarısı ve fonksiyonel durum açısından fark olmadığını göstermektedir.

Anahtar Kelimeler: Anemi, ferrik karboksimaltoz, kronik tromboembolik pulmoner hipertansiyon, pulmoner arteriyel hipertansiyon, pulmoner hipertansiyon

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Iron metabolism is an essential part of oxygen utilization in the body, and it also has important functions in DNA synthesis and cell progression.[1] Several lines of evidence indicate that abnormal iron handling frequently complicates pulmonary hypertension (PH).[2,3] Iron deficiency in patients with PH has been shown to cause functional capacity limitation and poor outcomes, even in the absence of anemia.[4] Accordingly, the iron replacement has been shown to improve functional capacity in some subgroups.[5,6]

Although preliminary results are promising for the use of iron replacement as a complementary treatment in PH treatment, most of the literature examining the effects of abnormal iron handling on the progression of PH concentrates on group 1 PH.[5,6] Since PH is a diverse group, whether the evidence acquired from group 1 PH could be applied to another PH subgroup is not known.[7] Indeed, the mechanism of iron deficiency in group 1 may be different from other groups. For example, group 4 PH patients, in whom life-long anticoagulation therapy is strongly indicated, may be prone to iron deficiency due to other mechanisms that are responsible for the abnormal iron handling in group 1 PH, such as chronic blood loss. On the other hand, some specific therapies used in group 1 PH patients, such as endothelin receptor antagonists, can cause abnormal iron metabolism, which is not relevant to the patients in other PH groups.[8]

In this study, we sought to explore whether there is a difference in response to iron replacement in patients with group 1 and group 4 PH, in terms of treatment success and functional status.

Methods

The study was undertaken at a tertiary referral center for pulmonary hypertension. Approval for this study was obtained from the Ethics committee of Marmara University Faculty of Medicine and the study was undertaken in accordance with the declaration of Helsinki.

Between January 2018 and January 2021, all patients who were admitted to our PH outpatient clinic with an established diagnosis of group 1 or group 4 PH and who were under stable treatment were retrospectively screened. The patients with a serum ferritin <100 ng/mL or a serum ferritin of 100-300 ng/mL in combination with a transferrin saturation (TSAT) <20% and received ferric carboxymaltose (FCM) treatment were included in the study.[9,10] The patients with significant liver (serum transaminases >3 times of the upper limit of normal) or kidney disease (creatinine clearance <30 mL/min/1.73 m^2), marked anemia (hemoglobin <7.5 mg/dL), or marked inflammation (C-reactive protein >25 mg/L) were excluded. Also, the patients with a history of hospitalization related to Pulmonary Arterial Hypertension (PAH) or any change in PAH therapy within 3 months or any iron therapy and/or blood transfusion within 12 weeks of first visit were excluded. Baseline characteristics, laboratory and hemodynamic parameters, and treatment information were obtained via chart review from the electronic hospital database.

Right Heart Catheterization

The diagnosis of PH was according to the Sixth World Symposium on Pulmonary Hypertension, based on a mean pulmonary arterial pressure (mPAP) of ≥20 mmHg that was demonstrated with right heart catheterization (RHC). Right heart catheterization was performed by a Swan Ganz catheter using jugular venous access with hemodynamic and fluoroscopic guidance for all patients. Measurements were obtained at end-expiration and averaged over 3-5 beats. Pulmonary vascular resistance (PVR) was calculated as mPAP minus mean pulmonary capillary wedge pressure divided by cardiac output (CO). Cardiac output was measured by indirect Fick method.

Treatment and Follow-up

Patients received a single infusion containing 500-1000 mg of FCM, not exceeding a total of 15 mg of iron per kg of body weight. The exact dose was calculated by Ganzoni's formula.[11] The respective dosages of concentrated FCM (available in 10 mL bottles of 50 mg iron/mL) were diluted in 100 mL sterile 0.9% sodium chloride solution and infused over a period of 15 minutes. The change in ferritin levels and TSAT were calculated at 12- and 24-week follow-up. A 6-minute walk test (6MWT), which was performed by the same nurse, is done at the first, 12-, and 24-week follow-up visits. No treatment change was done during 24-week follow-up period in the PH-related regimen.

Statistical Analysis

Baseline characteristics were summarized using standard descriptive statistics. Continuous variables were expressed as median ± interquartile range (IQR). Comparisons of relevant parameters between groups were performed by chi-square, Fisher's exact test, Mann–Whitney *U*, and Student's *t*-test, as appropriate. A paired-samples *t*-test was used to determine whether there was a statistically significant mean difference between baseline, 12-, and 24-week values in hematologic indices, NT-proBNP, and 6MWT results. Independent samples *t*-test was used to compare the change in ferritin and TSAT among groups. A Spearman's correlation test was run to assess the relationship between 6MWT and TSAT, ferritin, and NT-proBNP levels after preliminary analyses showed the relationships to be monotonic, as assessed by visual inspection of scatterplots. Statistical analyses were performed with Statistical Package for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA).

Results

In the predetermined study period, we identified 217 eligible patients with group 1 or 4 PH. A total of 72 patients met the inclusion criteria and 14 patients were excluded due to various reasons (Figure 1). Therefore, the final study population consisted of 58 patients. The baseline characteristics are presented

ABBREVIATIONS

CO	Cardiac output
CPET	Cardiopulmonary exercise test
CTEPH	Chronic thromboembolic pulmonary hypertension
FCM	Ferric carboxymaltose
IQR	Interquartile range
mPAP	Mean pulmonary arterial pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
TSAT	Transferrin saturation

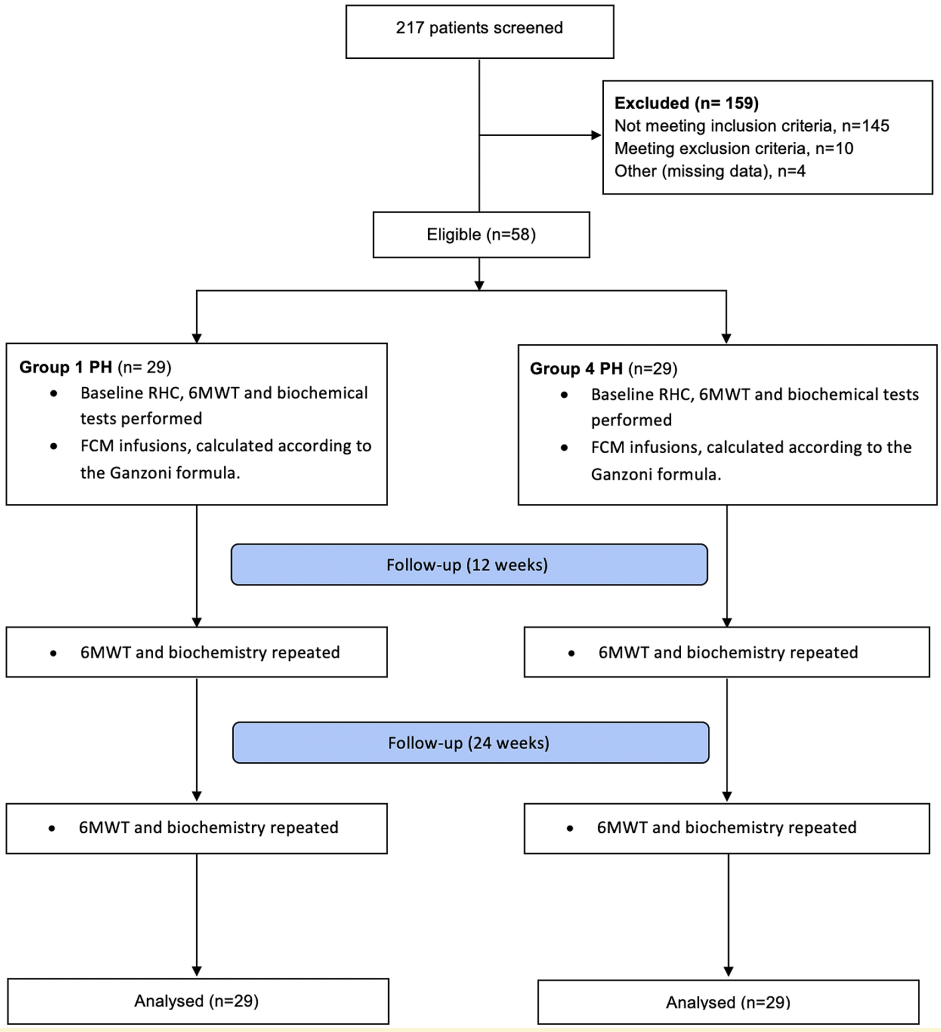

Figure 1. Patient enrollment flow chart. 6MWT, 6-minute walk test; FCM, ferric carboxymaltose; PH, pulmonary hypertension; RHC, right heart catheterization.

in Table 1. The baseline treatment is also summarized in Table 1. Of note, 41.3% (12/29) of the patients with group 4 PH had a history of pulmonary endarterectomy, 58.3% (7/12) of whom underwent balloon angioplasty due to residual PH or recurrent embolism, and 58.6% (17/29) patients were not considered suitable for balloon angioplasty or surgery. Baseline RHC parameters are summarized in Table 2. The time from the RHC to the first FCM application was 8.4 ± 0.19 months.

In group 1 PH patients, ferritin levels increased to 119 ng/mL at 12 weeks (from 14 ng/mL to 133 ng/mL, $P < .001$) and to 76 ng/mL at 24 weeks compared to baseline (from 14 ng/mL to 90 ng/mL, $P < .001$). In group 4 PH patients, ferritin levels increased to 112.9 ng/mL at 12 weeks (from 22.1 ng/mL to 145 ng/mL, $P < 0.001$) and 67.9 ng/mL at 24 week (from 22.1 ng/mL to 90 ng/mL, $P < .001$). Similarly, TSAT was significantly higher in both groups at 12 weeks (increased from 14.5% to 27.0% in group 1 PH patients, $P < .001$ and increased from 14.3% to 23.8% in group 4 PH patients, $P < .001$) and at 24 weeks compared to baseline (24.4%; $P < .001$, and 22.4%; $P < .001$, respectively) (Table 3). These changes were not statistically significant between groups for neither ferritin nor TSAT.

The total number of the patients with and without iron deficiency at 12 and 24 weeks is presented in Figure 2.

Correspondingly, the median (IQR) 6MWT distances were 356 (210) m, 412 (187.5) m, and 350 (195) m in group 1 PH patients and 260 (202.5) m, 315 (186.5) m, and 290 (180) m in group 4 PH patients. Although the difference between baseline and 12-week 6MWT was significant in both groups ($P < .001$ for both), this difference was lost at 24 weeks ($P = .519$ and $P = .073$, respectively) (Figure 3). The median (IQR) serum NT-proBNP levels were 243 (1055) ng/L, 306 (1233) ng/L, and 288 (1016) ng/L in group 1 PH patients and 628 (1884) ng/L, 750 (1266.5) ng/L, and 550 (1426.5) ng/L in group 4 PH patients. There was no difference in NT-proBNP levels between baseline and 12 weeks or baseline and 24 weeks in group 1 PH patients ($P = .507$ and $P = 0.830$, respectively). However, the increase and decrease in NT-proBNP levels were significant in group 4 PH patients at 12 and 24 weeks ($P = .004$ and $P = .011$, respectively).

The 6MWT distance was moderately correlated with TSAT levels at 12 weeks ($r_s = 0.528$, $P = .003$) and at 24 weeks ($r_s = 0.683$, $P < .001$) in group 1 PH patients but not with ferritin or NT-proBNP.

Table 1. Baseline Characteristics*

	Group 1 PH (n=29)	Group 4 PH (n=29)	P
Age, years	45.5 (30)	67 (23)	<.001
Male sex	7 (24.1)	4 (13.8)	.504
BMI, kg/m^2	26 (18)	29.45 (7)	.011
Hypertension	5 (17.2)	19 (65.5)	<.001
Diabetes	3 (10.3)	7 (24.1)	.297
CAD	0 (0)	5 (17.2)	N/A
Hypothyroidism	6 (20.7)	7 (24.1)	.755
AF	4 (13.8)	6 (20.7)	.730
Etiology of PAH			
-Idiopathic PAH	13 (44.8)		
-Connective tissue disease	7 (24.1)		
-Congenital heart disease	9 (31)		
SBP, mmHg	121.7 (31)	134 (24.5)	.023
WHO functional class			
II	8 (27.6)	8 (27.6)	1.0
III	21 (72.4)	21 (72.4)	
6MWT, m	356 (210)	260 (202)	.227
Laboratory parameters			
Creatinine, mg/dL	0.78 (0.32)	1.09 (0.48)	.001
NT-proBNP, ng/L	243 (1055)	628 (1884)	.349
CRP, mg/L	4 (2)	4 (1.5)	.608
Treatment			
ERA	4 (13.8)	0 (0)	N/A
ERA plus PDE5i	25 (86.2)	0 (0)	N/A
Riociguat	0 (0)	29 (100)	N/A
Anticoagulation	4 (13.7)	29 (100)	<.001
Diuretics	22 (75.9)	19 (65.5)	.391
Oxygen supplement	4(13.8)	6(20.7)	.278
Treatment duration, months	63.6 (21)	55.3 (32)	.068

*Data are presented as median (interquartile range) and n (%).
6MWT, 6-minute walk test; AF, atrial fibrillation; BMI, body mass index, CAD, coronary artery disease; CRP, C-reactive protein; ERA, endothelin receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; N/A, not applicable; PDE5i, phosphodiesterase type-5 inhibitor; PH, pulmonary hypertension; SBP, systolic blood pressure; WHO, World Health Organization.

The change in 6MWT also showed a weak correlation with the change in TSAT at 12 weeks (r_s=0.378, P = .043), although this correlation was lost at 24 weeks (r_s=0.104, P = .592). In group 4 PH patients, the 6MWT distance was not correlated with ferritin or TSAT. Although there was a moderate correlation between TSAT and NT-proBNP at 12 weeks (r_s=−0.686, P < .001) and at 24 weeks (r_s=0.447, P = .015), the change in TSAT and the change in NT-proBNP were not significantly correlated in both time points. Similarly, there was a moderate correlation between 6MWT distance and NT-proBNP at 12 weeks (r_s=−0.686, P < .001) and at 24 weeks (r_s=0.613, P < .001), and the change in 6MWT and the change in NT-proBNP were not significantly correlated in both time points.

Table 2. Baseline Hemodynamic Parameters*

	Group 1 PH	Group 4 PH	P
mPAP, mmHg	40 (27.5)	39 (12.75)	.093
P_{RA}, mmHg	8 (5)	11.5 (6)	.255
PVR, dyne/s/cm^5	456 (588)	384 (220)	.185
CO, L/min	4.89 (2.25)	4.62 (1.78)	.380
CI, L/min/m^2	3.08 (1.21)	3.01 (1.05)	.187
Arterial O_2 saturation, %	93 (6)	92 (6)	.627
MvO_2, %	70 (13.5)	65 (8.25)	.007

*Data are presented as median (interquartile range) and n (%).
CI; cardiac index; CO, cardiac output; mPAP, mean pulmonary arterial pressure; MvO_2, mixed venous saturation; P_{RA}, right atrial pressure, PVR, pulmonary vascular resistance.

Discussion

Several studies have reported that iron deficiency is common in PH, affecting nearly half of the patients, and is associated with diminished functional capacity and increased mortality.[12-14] Iron-deficient patients have a more severe phenotype, with worse functional class, higher mPAP, lower cardiac index, and raised NT-proBNP levels compared to their iron-replete counterparts.[13] Some evidence supports that iron replacement improves

Table 3. Hematologic Parameters at Baseline and Follow-Up*

	Group 1 PH	Group 4 PH	P
Hb, g/dL			
Baseline	12.7 (3.3)	11.9 (2.7)	.068
12 weeks follow-up	14 (2.75)	12.8 (2.5)	.038
24 weeks follow-up	13.4 (2.75)	12.8 (2.5)	.072
Hct, %			
Baseline	39 (8.95)	36.4 (7.4)	.081
12 weeks follow-up	41.5 (7.95)	38.1 (5.9)	.056
24 weeks follow-up	39.4 (8.3)	38 (6.2)	.110
RBC, mm^{-3}			
Baseline	4.7 (0.7)	4.3 (0.6)	.011
12 weeks follow-up	4.8 (0.75)	4.6 (0.8)	.504
24 weeks follow-up	4.6 (0.68)	4.5 (0.75)	.435
MCV, fL			
Baseline	84 (7.5)	82 (8.75)	.365
12 weeks follow-up	86.7 (4.6)	84.6 (7)	.505
24 weeks follow-up	86.5 (5.5)	85.6 (6)	.405
Ferritin, ng/mL			
Baseline	14 (45.65)	22.1 (35.75)	.613
12 weeks follow-up	133.8 (117.25)	145 (78.75)	.741
24 weeks follow-up	90 (143.15)	88.9 (42.25)	.476
TSAT, %			
Baseline	14.5 (17)	14.3 (13)	.642
12 weeks follow-up	27.0 (22)	23.8 (19)	.707
24 weeks follow-up	24.4 (17.3)	22.4 (13.0)	.491
NT-proBNP			
Baseline	243 (1055)	628 (1884)	.656
12 weeks follow-up	306 (1233)	750 (1266)	.324
24 weeks follow-up	288 (1016)	550 (1426)	.391

*Data are presented as median (interquartile range).
Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; RBC, red blood cell count; TSAT, transferrin saturation.

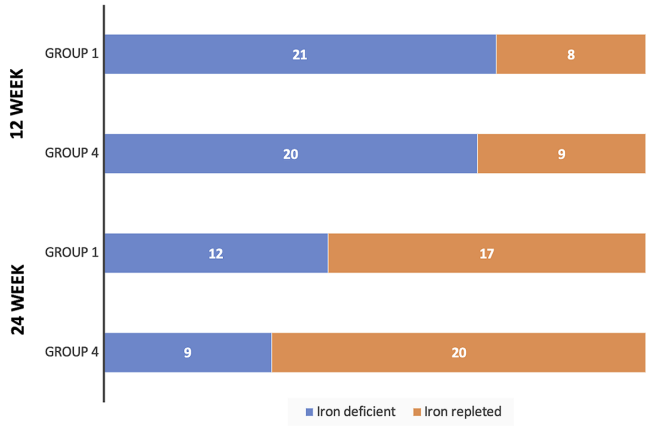

Figure 2. The total number of the patients with and without iron deficiency as defined by a serum ferritin <100 ng/mL or a serum ferritin of 100-300 ng/mL in combination with a transferrin saturation (TSAT) <20% at 12 and 24 weeks.

outcomes in some PH subsets.[15,16] Ruiter et al[5] investigated the use of intravenous iron therapy in group 1 PH patients and found that iron therapy may improve exercise capacity. They concluded that this beneficial effect could not be explained by an improved right ventricular function alone; they claimed that it might be related to increased muscle oxygen handling. Similarly, Viethen et al[6] demonstrated that FCM significantly improves exercise capacity and quality of life in patients with group 1 PH. Tay et al[15] replicated these findings in 25 iron-deficient cyanotic congenital heart disease patients. Ghio et al[16] showed that oral sucrosomial iron has beneficial effects in group 1 PH patients. However, PH has a diverse etiology and the underlying cause of iron deficiency may vary among different PH groups. To our knowledge, our study is the first to compare the effects of iron replacement in group 1 and group 4 patients. Our results indicate that iron replacement with FCM increases ferritin and TSAT levels in patients with both group 1 and group 4 PH. These increases also translated into a better functional capacity at 12 weeks, as indicated by an increase in 6MWT distances.

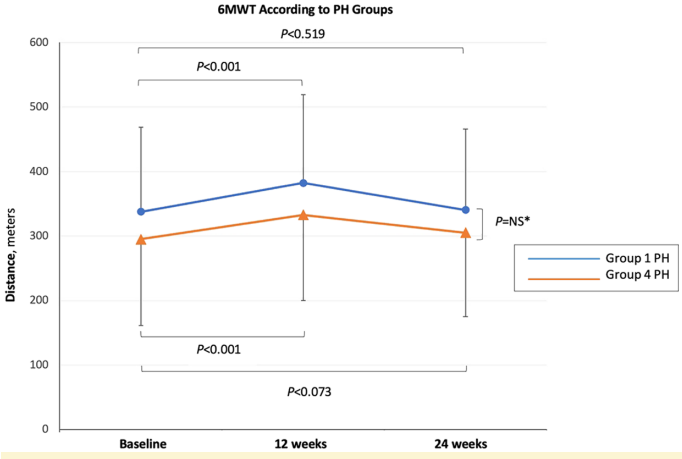

Figure 3. Six-minutes walk test (6MWT) distances in different time points according to the PH groups. PH, pulmonary hypertension. *P values are not significant (NS) in all 3 time points.

Several mechanisms may be responsible for the development of iron deficiency, including low absorption from the gut due to concomitant involvement of intestinal mucosa[17] or high blood levels of uptake inhibitors (such as hepcidin)[12]; increased iron loss due to chronic blood loss, abnormal iron handling due to PH-specific drugs,[8] or high iron use due to increased erythropoiesis.[18] On the other hand, abnormal iron handling itself may exacerbate many different pathophysiologic processes in PH. Iron deficiency has been shown to induce pulmonary vascular cell proliferation and remodeling.[19] Some evidence suggests that iron-deficient subjects may exhibit an exaggerated constrictive response to hypoxia that can be reversed by iron replacement.[20] Low levels of intracellular iron may compromise mitochondrial respiration and cause cardiomyocyte dysfunction which may potentiate the hemodynamic load of PH on right ventricle.[21] These mechanisms may differ among PH subgroups, but it is hard to speculate on with the very limited data at hand.

Although limited, our results hint that the cause of iron deficiency and the beneficial effects of iron replacement might also vary among different PH groups. For example, in our study, the absolute values of and the increase in TSAT showed some correlation with 6MWT distance in group 1 patients, but this association was not seen in group 4 PH patients. On the other hand, there was a correlation between NT-proBNP levels and 6MWT distance in group 4 PH patients, although the change in NT-proBNP did not show such a relationship with the change in 6MWT distance. It has been reported that iron deficiency is more prevalent in patients with group 1 PH compared to patients with group 4 PH, which was partly explained by increased IL-6 and hepcidin in group 1 PH patients.[14] This difference may indeed indicate a genuine distinction in pathophysiology, as BMPR2 gene mutation and/or subsequent downstream pathway dysfunction are implicated both in the pathogenesis of group 1 PH and altered iron handling due to increased hepcidin synthesis.[22] On the other hand, the correlation between NTproBNP and better functional capacity in group 4 patients may be related to better right ventricular function, since iron replacement has been shown to improve right ventricular ejection fraction.[23] Further studies are needed to shed light on underlying pathophysiologic differences.

Another interesting finding of our study is that the positive effect of iron replacement on iron stores endures at 24 weeks; however, the beneficial effect seen on the functional capacity is lost at 24 weeks. This may indicate that abnormal intracellular iron handling may not be immediately reflected by the blood levels. Long-term studies are needed to elucidate whether iron replacement has a sustained positive effect in patients with PH or needs early replacement without waiting for the iron stores to be depleted. Another possibility is that the exercise stress posed by the 6MWT may be insensitive to minor improvements and/or changes in exercise capacity. In a previous study by Ruiter et al[5] the achieved distance in the 6MWT was unchanged by iron therapy, whereas there was a significant improvement in exercise endurance time and aerobic capacity in the submaximal cardiopulmonary exercise test (CPET). The authors suggested that this apparent contradiction may have stemmed from the difference in the accuracy of and the type of exercise used in these 2 tests. In addition, the 6MWT has been related to less metabolic stress and a higher aerobic capacity compared to the CPET.[24]

There are several limitations to our study. Firstly, the study size is limited. The selection of a relatively stable subgroup may have led to the underrepresentation of the patients with more severe disease and precluded the exploration of some possible drug interactions. For instance, none of the patients included in the study was WHO class IV nor was taking prostanoid treatment. Furthermore, group 1 PH includes a diverse group of different etiologies which may have differing effects on iron metabolism. But, the small size of our study did not permit us to dissect the effects of iron replacement in these subgroups. The effects of iron replacement on right ventricular function and the change in hemodynamics could not be evaluated. Although we speculate the possible effects of iron replacement extending beyond the simple replenishment of iron stores, our study cannot provide direct evidence for clarifying these factors. However, the apparent diminishing effect of iron replacement on 6MWT may have been confounded by other factors including the progression of the underlying disease. Further studies are needed to elucidate the complete underlying pathophysiology of iron replacement on functional status.

In conclusion, our study indicates that there is no difference in response to iron replacement in patients with group 1 and group 4 PH, in terms of treatment success and functional status. However, further studies are needed to elucidate if the underlying cause of iron deficiency and the beneficial effects of iron replacement differ between these subgroups.

Ethics Committee Approval: Approval for this study was obtained from the Ethics committee of Marmara University Faculty of Medicine (No: 09.2021.1111).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-Review: Externally peer-reviewed.

Author Contributions: Concept – D.A., E.A.; Design – E.A., D.A.; Supervision – B.M., B.Y.; Resources – D.A., D.K.; Materials – D.A., D.K., B.K.; Data Collection and/or Processing – D.A., B.K.; Analysis and/or Interpretation – E.A., D.A.; Literature Search – D.A., E.A.; Writing Manuscript – E.A., D.A.; Critical Review – B.M., B.Y.

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