Iron deficiency in systemic sclerosis patients with and without pulmonary hypertension

Gerrina Ruiter1,2, Irene J. Lanser1, Frances S. de Man1, Willem J. van der Laarse2, John Wharton3, Martin R. Wilkins3, Luke S. Howard4, Anton Vonk-Noordegraaf1 and Alexandre E. Voskuyl5

Abstract

Objectives. SSc-associated pulmonary hypertension (SSc-PH) has a worse prognosis compared with SSc without PH (SSc-nonPH). Iron deficiency (ID) was previously associated with worse clinical outcome and survival in other types of PH, but ID effects in SSc-PH are unknown. Therefore we investigated the prevalence and clinical significance of ID in systemic sclerosis patients with and without PH.

Methods. Body iron status was determined in SSc-PH (n = 47) and SSc-nonPH patients (n = 122). ID was defined by circulating soluble transferrin receptor (sTfR) levels > 28.1 nmol/l. Clinical and exercise parameters were compared between the groups. Four-year survival after iron measurements was determined.

Results. ID prevalence was 46.1% in SSc-PH compared with 16.4% in SSc-nonPH patients (P < 0.001). Overall hepcidin levels were high compared with reference values and related to sTfR, but not with IL-6 (P = 0.82). Six-minute walking distance and maximal achieved work at ergometry was lower in SSc-PH compared with SSc-nonPH patients (P < 0.001 and P < 0.01, respectively) and was even further reduced in case of ID (Pinteraction < 0.05). In addition, ID SSc-PH patients had a poorer survival compared with non-ID patients [hazard ratio (HR) 0.34, 95% CI 0.14, 0.82, P < 0.05] and a similar trend was observed in SSc-nonPH patients (HR 0.16, 95% CI 0.02, 1.11, P = 0.06).

Conclusion. ID is more prevalent in SSc-PH than in SSc-nonPH patients and is associated with exercise impairment in both SSc-PH and SSc-nonPH. In addition, ID SSc-PH patients have a significantly worse survival compared with non-ID patients.

Key words: hepcidin, iron metabolism, exercise capacity.

Introduction

SSc is a chronic disease characterized by progressive collagen production, endothelium dysfunction, chronic inflammation and autoantibody production [1, 2]. Pulmonary hypertension (PH) can develop in the course of this disease and is currently the leading cause of death in SSc patients, with a reported 3-year survival of 47–56%, despite therapy [3–7]. Also, compared with other types of PH, SSc-associated PH (SSc-PH) has a more severe manifestation and poorer prognosis and current therapy is primarily aimed at improving quality of life and right ven- tricular function [1, 8]. Recently there has been increasing interest in improving exercise capacity with iron supplementation in iron-deficient idiopathic pulmonary arterial hypertension (IPAH) patients [9]. This has evolved from the finding that IPAH patients have a high prevalence of iron deficiency (ID), which is associated with poor survival and worse clinical performance and exercise capacity [10–12]. The development of ID in IPAH has been related to disproportionately high hepcidin levels, which reduces iron absorption from the gut and iron release from iron-containing cells [13]. Hepcidin is produced in the liver and
is regulated via different pathways by extra- and intracellular iron levels [13]. Normally when ID is present, hepcidin production in the liver is inhibited, thereby increasing iron release from iron-containing cells [13]. However, whether ID is also common in SSc-PH, is related with hepcidin levels and has detrimental effects on clinical outcome is unknown.

Therefore the aim of this study was 2-fold: (i) to investigate the prevalence of ID in SSc-PH compared with SSc patients without PH (SSc-nonPH) in relation to hepcidin levels and (ii) to assess the impact of ID on clinical performance and outcome in an important clinical subtype of PH.

Methods

Patient inclusion

Patients with SSc from whom a plasma sample was collected in heparin and EDTA tubes between June 2005 and April 2011 and stored in the biobank of the Department of Rheumatology at −80°C were considered for the present study. In addition, SSc patients who were primarily referred to the Department of Pulmonology for investigation of PH were also included. The study was approved by the local medical ethics committee (Institutional Review Board on Research Involving Human Subjects, Amsterdam, The Netherlands) and all patients gave written informed consent according to the Declaration of Helsinki.

Samples were included for the current analysis when the patients were classified with limited cutaneous systemic sclerosis (LcSSc) or diffuse cutaneous systemic sclerosis (DcSSc) according to the criteria of LeRoy et al. [14]. Patients had to be clinically stable in the previous 3 months and haematology laboratory results of at least haemoglobin, haematocrit and mean corpuscular volume were required. Patients with overt iron-causing comorbidities such as gastrointestinal (GI) blood loss as observed with upper endoscopy or colonoscopy, gynaecological blood loss or the presence of other haematological diseases at the time of sampling were excluded. The diagnosis of PH was defined by mean pulmonary arterial pressure >25 mmHg, measured by right heart catheterization [15]. One hundred and sixty-nine patients were classified as SSc and met the inclusion criteria. Medical charts were systematically assessed and SSc characteristics, comorbidities as well as medical treatment were recorded. Right heart catheterization data, 6-min walking distance (6MWD) from a 6-min walking test (6MWt), pulmonary function test data and cardiopulmonary exercise test (CPET) data at the time of plasma sampling were collected.

Serum iron parameters

From 82 patients, serum iron parameters [serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin levels] were measured at the time of blood sampling. From the remaining 87 patients, retrospective iron measurements were performed. Serum iron and TIBC were determined using photometry (Modular P800 system, Roche, Almere, The Netherlands). Transferrin saturation was calculated from serum iron divided by TIBC. Sandwich immunoassays with electrochemical luminescence technology were used to measure serum ferritin levels (Modular E170 system, Roche). From all patients, circulating soluble transferrin receptor (sTfR), IL-6 and serum hepcidin levels were measured in EDTA samples. sTfR and IL-6 were measured with ELISA (R&D Systems Europe, Abingdon, Oxfordshire, UK) and hepcidin concentration was determined by a competitive radioimmunoassay [16]. ID was defined as sTfR levels >28.1 nmol/l as described previously [10]. This parameter provides a more reliable method to determine ID than serum ferritin, since the production of the receptor is not influenced by inflammation or infection [17].

Statistical analysis

All data were verified for normal distribution and transformed when necessary. For comparisons, two-tailed unpaired Student t-tests, Fisher’s exact tests or chi-square tests were performed. Two-way analysis of variance (ANOVA) with Bonferroni post hoc tests was done to measure differences between the ID and non-ID SSc-PH and SSc-nonPH patients. Correlations were carried out with Pearson’s linear regression. The association of PH and other parameters with ID was tested with univariate logistic regression analysis with subsequent correction for confounding effects. Kaplan–Meier survival was stratified by the presence or absence of ID and compared by log-rank tests within the SSc-PH and SSc-nonPH patients. Survival was measured from the time of sampling to the 48-month follow-up. Analyses were performed with GraphPad Prism 5.00 (GraphPad Software, San Diego, CA, USA) or SPSS 20.0 (SPSS Inc., Chicago, IL, USA). All data are represented as mean (±S.D.) unless stated otherwise and a P-value < 0.05 is considered statistically significant.

Results

ID is more prevalent in SSc-PH than in SSc-nonPH

PH was present in 27.8% (47/169) of patients with SSc. Detailed clinical data on SSc-PH and SSc-nonPH patients are shown in Table 1. Compared with SSc-nonPH, SSc-PH patients were more often diagnosed with LcSSc, were older, had a longer duration of RP and SSc disease and had a lower Rodnan skin score, as expected. The percentage of SSc organ involvement was similar in the two groups. More often SSc-PH patients had ACA and less often anti-Scl-70 antibodies compared with SSc-nonPH patients.

ID was more prevalent in SSc-PH (22/47 patients, 46.1%) compared with SSc-nonPH (20/122 patients, 16.4%, P < 0.001 vs SSc-PH). In addition, PH was associated with a higher risk of having ID [odds ratio (OR) 4.49, 95% CI 2.13, 9.47, P < 0.001] as well as age, oxygen saturation, use of anticoagulants, hepcidin and IL-6 values (Table 2). After correction for significant confounding effects of age and serum hepcidin concentration, PH...
was still associated with a higher risk of ID (OR 2.49, 95% CI 1.03, 6.00, \( P < 0.05 \)). Furthermore, ID patients had a significantly poorer survival in the SSc-PH group compared with the non-ID patients (hazard ratio (HR) 0.34, 95% CI 0.14, 0.82, \( P < 0.05 \)) (Fig. 1). A similar trend was observed in SSc-nonPH patients (HR 0.16, 95% CI 0.02, 1.11, \( P = 0.06 \)).

**ID is associated with hepcidin levels**

Table 3 shows serum iron parameters from SSc-PH and SSc-nonPH patients divided by the presence or absence of ID. As expected, both ID groups had significantly higher sTfR levels and lower serum iron, transferrin saturation and ferritin levels compared with non-ID patients. Mean hepcidin values were significantly lower in both ID groups compared with non-ID patients (Fig. 2A) and IL-6 values were similar in all groups (Fig. 2B). Higher sTfR levels were associated with a lower hepcidin concentration (Fig. 2C). Interestingly, there was no correlation between hepcidin concentration and IL-6 values (\( R = 0.012, P = 0.90 \); Fig. 2D) or with hepcidin and CRP levels (\( R = 0.049, P = 0.57 \); Fig. 2E).

**Cardiac function in SSc-PH is unaffected by ID**

Right heart catheterization data was available from 46 of 47 SSc-PH patients with a median of 3 days before or after blood sampling (Table 1). Five patients had a pulmonary capillary wedge pressure >15 mmHg (range 16–19 mmHg). Except for heart rate, which was higher in ID compared with non-ID SSc-PH patients [84 (16) vs 74 (13) bpm, \( P < 0.05 \)], all haemodynamic parameters were similar for non-ID and ID patients (details are provided in supplementary Table S1, available at Rheumatology Online) with a trend (\( P = 0.09 \)) towards a higher cardiac function in SSc-PH patients.
output in the ID patients. Eight ID and 11 non-ID SSc-PH patients were PH treatment naive. Prescriptions for prostanoids (1 vs 0), endothelin receptor antagonists (6 vs 6), phosphodiesterase type 5 inhibitors (4 vs 2) and combination or triple therapy (3 vs 6) were similar in ID vs non-ID SSc-PH patients.

Exercise capacity is reduced in ID in both SSc-nonPH and SSc-PH

Pulmonary function tests show that SSc-PH patients had worse pulmonary function compared with SSc-nonPH patients (details are presented in supplementary Table S2, available at Rheumatology Online). In addition, CPET revealed lower maximum achieved work, maximal oxygen consumption, maximal heart rate, oxygen pulse and saturation with higher minute ventilation as a percentage of predicted in SSc-PH compared with SSc-nonPH patients (supplementary Table S2, available at Rheumatology Online). Furthermore, SSc-PH patients had a significantly lower 6MWD compared with SSc-nonPH [316 (137) vs 474 (120) m, P < 0.001].

In SSc-nonPH, but not in SSc-PH patients, ID was associated with a further reduction in pulmonary function (supplementary Table S3, available at Rheumatology Online). ID resulted in lower maximal work in SSc-nonPH [non-ID 74.9 (29.9) vs ID 43.3 (24.4) W, P < 0.01], but not in SSc-PH patients [non-ID 55.1 (24.5) vs ID 39.8 (19.5) W]. After correction for age, gender and BMI, maximal work was also decreased in SSc-PH with ID [non-ID 60.2 (30.1) vs ID 41.2 (18.9)% of predicted, P < 0.05] but not in SSc-nonPH [non-ID 66.2 (29.7) vs ID 52.7 (31.5)% of predicted] (Fig. 3A and B; supplementary Table S3, available at Rheumatology Online). ID patients were shown to have further reduced 6MWD in both SSc-nonPH [non-ID 489 (113) vs ID 396 (128) m, P < 0.05] and SSc-PH patients [non-ID 356 (118) vs ID 270 (145) m, P < 0.05]. After correction for age, gender and BMI, ID SSc-PH patients still had a worse outcome compared with non-ID

### Table 2: ID-causing factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>4.488</td>
<td>2.126, 9.473</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.327</td>
<td>0.500, 3.518</td>
<td>0.570</td>
</tr>
<tr>
<td>Age</td>
<td>1.043</td>
<td>1.013, 1.074</td>
<td>0.004</td>
</tr>
<tr>
<td>LcSSc vs DcSSc</td>
<td>0.777</td>
<td>0.310, 1.947</td>
<td>0.590</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.002</td>
<td>0.950, 1.057</td>
<td>0.935</td>
</tr>
<tr>
<td>GI involvement</td>
<td>0.919</td>
<td>0.413, 2.042</td>
<td>0.835</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>3.913</td>
<td>1.866, 8.206</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAIDs use</td>
<td>0.836</td>
<td>0.347, 2.014</td>
<td>0.690</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>0.814</td>
<td>0.814, 0.983</td>
<td>0.020</td>
</tr>
<tr>
<td>Hepcidin a</td>
<td>0.494</td>
<td>0.361, 0.675</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 a</td>
<td>1.464</td>
<td>1.071, 2.002</td>
<td>0.017</td>
</tr>
<tr>
<td>Logistic regression analysis corrected for age (years)</td>
<td>3.460</td>
<td>1.536, 7.798</td>
<td>0.003</td>
</tr>
<tr>
<td>Logistic regression analysis corrected for hepcidin concentration a (ng/ml)</td>
<td>3.497</td>
<td>1.570, 7.786</td>
<td>0.002</td>
</tr>
<tr>
<td>Logistic regression analysis corrected for both age and hepcidin concentration a</td>
<td>2.491</td>
<td>1.034, 5.999</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Outcome parameter: presence or absence of ID. Univariate logistic regression analysis was performed on parameters that interfere with the iron status. The influence of PH on the development of ID was tested with univariate logistic regression analysis with subsequent correction for confounding effects. Only age and hepcidin concentration were significant confounders on the effect of PH on ID. aLog transformed data.

**Fig. 1** Survival plot.

Kaplan–Meier survival plot of all patients with a total follow-up time of 48 months and t = 0 at the moment of blood sampling. ID SSc-PH patients had a worse survival compared with non-ID patients (HR 0.34, 95% CI 0.14, 0.82, P < 0.05) with a similar trend in SSc-nonPH patients (HR 0.16, 95% CI 0.02, 1.11, P = 0.06).
Iron deficiency in systemic sclerosis

Table 3 Serum iron parameters

<table>
<thead>
<tr>
<th></th>
<th>SSc-nonPH</th>
<th>SSc-PH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-ID (n = 102)</td>
<td>ID (n = 20)</td>
</tr>
<tr>
<td>CRP, mean (s.d.), mg/l</td>
<td>11.6 (26.0)</td>
<td>14.3 (19.5)</td>
</tr>
<tr>
<td>Haemoglobin, mean (s.d.), g/dl</td>
<td>13.0 (1.4)</td>
<td>12.0 (2.2)</td>
</tr>
<tr>
<td>Haematocrit, mean (s.d.), l/l</td>
<td>0.39 (0.04)</td>
<td>0.36 (0.06)</td>
</tr>
<tr>
<td>Mean corpuscular volume, mean (s.d.), fl</td>
<td>89.9 (4.7)</td>
<td>85.3 (6.4)</td>
</tr>
<tr>
<td>Creatinine, mean (s.d.), µmol/l</td>
<td>72 (17)</td>
<td>83 (33)</td>
</tr>
<tr>
<td>eGFR, mean (s.d.), ml/min/1.73 m²</td>
<td>82 (12)</td>
<td>76 (15)</td>
</tr>
<tr>
<td>NT-proBNP², mean (s.d.), ng/l</td>
<td>348 (653)</td>
<td>1074 (2422)</td>
</tr>
<tr>
<td>Serum iron, mean (s.d.), µmol/l</td>
<td>13.3 (5.7)</td>
<td>7.9 (4.3)³</td>
</tr>
<tr>
<td>TIBC², mean (s.d.), µmol/l</td>
<td>63.5 (10.4)</td>
<td>67.5 (12.1)</td>
</tr>
<tr>
<td>Transferrin saturation, mean (s.d.), %</td>
<td>21.2 (9.1)</td>
<td>12.0 (6.9)³</td>
</tr>
<tr>
<td>Serum ferritin, mean (s.d.), µg/l</td>
<td>106 (100)</td>
<td>51 (42)*</td>
</tr>
<tr>
<td>sTfR², mean (s.d.), nmol/l</td>
<td>20.4 (4.3)</td>
<td>34.5 (5.0)³</td>
</tr>
</tbody>
</table>

nID: non-iron deficient; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal prohormone of brain natriuretic peptide. *Log transformed data. All data were tested with ANOVA. *\(P < 0.05\), **\(P < 0.01\), ***\(P < 0.001\) vs non-ID patients.

Fig. 2 Hepcidin, IL-6 and sTfR levels in all patients.

(A) Hepcidin values are lower in the ID groups compared with the non-ID patients. Note that many non-ID SSc-nonPH patients have hepcidin levels above the upper limit of normal. (B) Although IL-6 levels are not different between the groups, the majority of the patients have increased IL-6 levels. (C) Higher sTfR (thus more ID) is associated with a reduction of hepcidin levels in both SSc-nonPH and SSc-PH patients. (D) Hepcidin concentration is not related to IL-6 levels or (E) CRP values. Every dot represents one patient. The dotted line represents the upper limit of normal. *\(P < 0.05\) and ***\(P < 0.001\).

SSc-PH patients (55.2 (28.2) vs 75.2 (21.0)% of predicted, \(P < 0.05\)) (Fig. 3C and D). Furthermore, it was demonstrated that a lower 6MWD is associated with higher sTfR levels \(r = 0.48, P < 0.001\).

Discussion

This study demonstrates a higher prevalence of ID in SSc-PH compared with SSc-nonPH patients, accompanied by
a worse survival rate after 4 years. In addition, ID is associated with lower exercise capacity in cycling and walking tests in all SSc patients irrespective of the presence of PH. The present study suggests that iron supplementation may also be important in iron-deficient SSc-PH and SSc-nonPH patients to improve clinical performance.

The prevalence of SSc-PH patients in the current cohort of SSc patients is greater than the 10% reported in literature [4, 18], which is most likely due to referral bias since our centre is a tertiary PH referral centre. The found prevalence of ID in SSc-PH patients of 46.1% is consistent with the reported prevalence of ID in IPAH (43-63%) [10, 12].

**Exercise capacity is reduced in iron deficiency**

Maximal work at CPET and the 6MWD was significantly reduced in SSc-PH compared with SSc-nonPH patients. Also, diffusion capacity was shown to be more severely reduced in SSc-PH, representing a greater right ventricular afterload and thereby impeding exercise. However, in both groups ID was associated with a reduction in exercise capacity, as was previously described in IPAH [11]. In the absence of haemodynamic differences between ID and non-ID SSc-PH patients, we postulate that the lower exercise capacity is caused by changes in oxygen handling of the skeletal muscle. Skeletal muscle myoglobin, which is an iron-containing oxygen transporter, was shown to be decreased in the case of high erythropoietic iron demand at high altitude in healthy volunteers [19]. Robach et al. [19] concluded that in iron-deficient circumstances, myoglobin releases iron in favour of haemoglobin production and tissue oxidative capacity reduces. It has been shown that ID anaemia reduced aerobic work capacity in animal and human studies [20]. In addition, ID without anaemia impaired adaptation in endurance capacity, thereby implicating that exercise capacity is indeed diminished in ID [21].

**Iron deficiency-inducing factors**

Several mechanisms are important in the development of ID, including low iron intake or uptake from the gut and increased iron loss or high iron use due to increased erythropoiesis. Since many SSc patients have a broad spectrum of symptoms due to GI involvement of the disease (e.g. esophagitis, dysmotility of the GI tract, watermelon stomach or gastric antral vascular ectasia, telangiectasia of the colon), it is plausible that they have lower iron intake or uptake and more GI iron loss [22]. Although we demonstrated that the percentage of patients with GI involvement of SSc was similar in SSc-nonPH and SSc-PH patients and all patients with known blood loss were excluded, this does not rule out that GI vascular telangiectasia or bleeding may be more severe in SSc-PH patients. In addition, anticoagulants were more often used by SSc-PH patients, possibly increasing the risk of iron loss from silent GI bleeding. However, to investigate whether the GI tract is indeed (partially) responsible for the high ID prevalence in SSc-PH patients...
requires a full GI physical exam and remains to be elucidated in the future.

Increased hepcidin levels alone are already associated with ID [23]. Normally hepcidin production in the liver results in reduced iron release from iron-containing cells and thereby lowers serum iron levels. Opposing mechanisms occur in case of low serum iron or high erythropoietic iron demand; hepcidin production is down-regulated, enabling iron release into the blood [13]. In the present study, a large number of patients showed increased levels of serum hepcidin, which may be driving the high ID prevalence. As expected, the ID patients had lower mean hepcidin values, although a substantial number of ID patients showed hepcidin levels above the upper limit of normal, which further limits iron availability.

Possible mechanisms of high hepcidin in SSc

The present study shows for the first time that hepcidin levels are increased in an SSc population. The mechanisms of this phenomenon need to be further elucidated. Hepcidin is produced in the liver, and although the liver can be affected in SSc, it was rare in the present cohort (n = 3). Furthermore, endothelin receptor antagonists used in PH treatment are known to alter liver function, which could indirectly influence hepcidin production. However, this does not explain the high hepcidin levels in SSc-nonPH patients. Hepcidin secretion is regulated by inflammation, particularly IL-6/signal transducer and activator of transcription 3 (STAT3) [24], and bone morphogenetic protein (BMP)/SMAD signalling [25], which are both perturbed in IPAH [26, 27]. In addition, IPAH patients with BMP type 2 receptor (BMPR-2) mutations appear to be affected in SSc, it was rare in the present cohort (n = 3). Furthermore, endothelin receptor antagonists used in PH treatment are known to alter liver function, which could indirectly influence hepcidin production. However, this does not explain the high hepcidin levels in SSc-nonPH patients. Hepcidin secretion is regulated by inflammation, particularly IL-6/signal transducer and activator of transcription 3 (STAT3) [24], and bone morphogenetic protein (BMP)/SMAD signalling [25], which are both perturbed in IPAH [26, 27]. In addition, IPAH patients with BMP type 2 receptor (BMPR-2) mutations appear to have a higher prevalence of ID compared with patients without a BMPR-2 mutation [12]. Although BMPR-2 mutations have not been found in SSc-PH patients, BMP signalling is shown to be generally perturbed in PH and may therefore contribute to high hepcidin levels [27–29]. On the other hand, inflammation-induced hepcidin expression might be important since IL-6 levels were increased in all patients [24]. Although it is possible that hepcidin expression may be stimulated by other inflammatory mediators, IL-6 is the only cytokine generally accepted to induce hepcidin expression in vitro and in vivo [13, 30]. Interestingly, although both IL-6 and hepcidin values were elevated, there was no association between the two factors in the current study population, as noted previously in IPAH [10, 12]. A possible explanation might be that erythropoietic inhibition of hepcidin overrules the inflammatory-mediated hepcidin production when both phenomena are present. This was previously shown by Theurl et al., who found similar IL-6 levels in humans with high and low hepcidin with different types of anaemia [31] and in IPAH, where high erythropoietin levels correspond with lower hepcidin levels [10].

Furthermore, chronic inflammatory diseases (i.e. SSc) are often accompanied by anaemia of chronic disease [32]. As part of this phenomenon, erythropoiesis is stimulated but iron incorporation into haemoglobin is disturbed and the life span of red blood cells is shortened, all factors that can contribute to the development of ID [33]. Finally, myeloid abnormalities have been described in IPAH and associated PAH patients, possibly leading to disturbed erythropoiesis and iron use [33].

Limitations

The study design did not permit conclusions about causal relations between PH and the presence of ID. In addition, the 6MWT is not an ideal test for exercise capacity in SSc since pain and musculoskeletal dysfunction confound the utility of the test [34]. However, despite the difficulties with this test, CPET measures were also significantly worse, thereby supporting the 6MWT findings.

Conclusions

From this study it is apparent that ID is more prevalent and reduced survival in SSc-PH compared with SSc-nonPH patients. In addition, ID is associated with lower exercise capacity in both SSc-PH and SSc-nonPH patients. Future studies are needed to investigate the causes of ID in SSc-PH and to reveal whether iron therapy can improve exercise capacity in ID SSc patients.

Rheumatology key messages

- Iron deficiency is highly prevalent in SSc-PH.
- In both SSc with and without PH, iron deficiency reduces exercise capacity.

Funding: This research was funded by The Netherlands Organization for Scientific Research (NWO VIDI grant 917.96.306) and BHF Programme grant RB/10/16/28575.

Disclosure statement: A.V.-N. has received lecture fees from Actelion, Bayer, GlaxoSmithKline, Lilly, United Therapeutics and Pfizer; is on industry advisory boards for Actelion, United Therapeutics, Novartis and Bayer and has served on steering committees for Actelion, GlaxoSmithKline, Bayer and Pfizer. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References


20 Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–88S.


27 Morell NW. Pulmonary hypertension due to BMPR2 mutation: a new paradigm for tissue remodeling? Thorac 2011;1206:800.


