

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A cross-sectional study of the prevalence and associations of iron deficiency in a cohort of patients with chronic obstructive pulmonary disease.
AUTHORS	Frise, Matthew; Nickol, Annabel; Cheng, Hung-Yuan; McGahey, Anne; McFadyen, Bethan; Harris-Wright, Tara; Bart, Nicole; Curtis, M; Khandwala, Shivani; O'Neill, David; Pollard, Karen; Hardinge, F; Rahman, Najib; Armitage, Andrew; Dorrington, Keith; Drakesmith, Hal; Ratcliffe, Peter; Robbins, Peter

VERSION 1 - REVIEW

REVIEWER	Donald Silverberg Dept of Nephrology Tel Aviv Medical Center Weizman Tel Aviv Israel
REVIEW RETURNED	07-Apr-2015

GENERAL COMMENTS	This is a useful contribution to the question of iron deficiency in COPD and will hopefully stimulate some intervention studies. The authors should touch on the limitations of the study.
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REVIEWER	Karina Portillo Hospital Germans Trias i Pujol Barcelona SPAIN
REVIEW RETURNED	16-Apr-2015

GENERAL COMMENTS	<p>This original article studies iron deficiency (ID) in COPD and their relationship with varying clinical variables, topic which have never been studied.</p> <p>The hypotheses and objectives of the study are well presented. Also the methods, population, design and statistical analysis of this study are appropriate to achieve the objectives.</p> <p>Minor comments</p> <p>Abstract : I suggest to include in the results the clinical findings of the study (patients with ID had more exacerbations and worse outcomes in the exercise test ,despite of the fact that these differences were not statistically significant. The conclusion must be consistent with these results. The authors pointed out that pulmonary hypertension in COPD is a possible consequence of iron deficiency, which is not a conclusion of the study itself and may</p>
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	<p>confuse the reader. To me, the authors did well in pointing this matter in the discussion, which is the corresponding section for this comment</p> <p>Methods: it would be convenient to specify that the diagnosis of COPD was made according to the latest guidelines GOLD by spirometry, and in accordance with the spirometric parameters the classification of severity was made. Please add the reference.</p> <p>The authors should specify why it was used as a measure of exercise tolerance the shuttle walk test instead of six minutes walking test. Also in the Results, should specify the meaning of short-burst oxygen home.</p> <p>Discussion: The term primary pulmonary hypertension is disused . Modify by idiopathic pulmonary hypertension. "In patients with primary pulmonary hypertension the prevalence of nonanaemic iron deficiency approaches two-thirds, and severity of iron deficiency correlates (pag.14)" It is important to highlight the clinical findings of this study, about exacerbations and exercise limitation, since exacerbations is one of the most important outcomes in the prognosis. There is no comparison with the studies available in the literature of worse prognosis in patients with COPD and anemia.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Donald Silverberg

1. This is a useful contribution to the question of iron deficiency in COPD and will hopefully stimulate some intervention studies. The authors should touch on the limitations of the study.

We thank the reviewer for this comment and share the hope that interventional studies will now follow. We highlight some of the limitations of the study in the “strengths and limitations of this study” section, but have revised the discussion to make these more obvious to the reader.

Reviewer 2 - Karina Portillo

This original article studies iron deficiency (ID) in COPD and their relationship with varying clinics variables, topic which have never been studied. The hypotheses and objectives of the study are well presented. Also the methods, population, design and statistical analysis of this study are appropriate to achieve the objectives.

1. Abstract: I suggest to include in the results the clinical findings of the study (patients with ID had more exacerbations and worse outcomes in the exercise test, despite of the fact that these differences were not statistically significant. The conclusion must be consistent with these results. The authors pointed out that pulmonary hypertension in COPD is a possible consequence of iron deficiency, which is not a conclusion of the study itself and may confuse the reader. To me, the authors did well in pointing this matter in the discussion, which is the corresponding section for this comment.

We thank the reviewer for suggesting these modifications to the abstract and have revised the results section of the abstract to include the result of significantly more self-reported exacerbations in the ID group and a non-significant difference in exercise tolerance. The reviewer highlights a source of possible confusion relating to pulmonary hypertension in the conclusion section of the abstract. We

have revised this accordingly so that mention is now made of the exacerbation and exercise results, whilst the reference to pulmonary hypertension is removed, since this is addressed in the discussion. We take the opportunity of mentioning that the BMJ Open Editorial Office also requested separately that the abstract be completely reformatted, and we have done as instructed.

2. Methods: it would be convenient to specify that the diagnosis of COPD was made according to the latest guidelines GOLD by spirometry, and in accordance with the spirometric parameters the classification of severity was made. Please add the reference. The authors should specify why it was used as a measure of exercise tolerance the shuttle walk test instead of six minutes walking test. Also in the Results, should specify the meaning of short-burst oxygen home.

We have added a reference to GOLD as requested. We have also explained why the SWT was used; this is in addition to the existing section in the discussion where the value of this test in COPD is already described. We have added a brief definition of short-burst home oxygen therapy for clarity.

3. Discussion: The term primary pulmonary hypertension is disused. Modify by idiopathic pulmonary hypertension. "In patients with primary pulmonary hypertension the prevalence of nonanaemic iron deficiency approaches two-thirds, and severity of iron deficiency correlates (pag.14)"

We have modified the two occurrences of "primary" in the text accordingly.

4. It is important to highlight the clinical findings of this study, about exacerbations and exercise limitation, since exacerbations is one of the most important outcomes in the prognosis.

We agree. The text has been revised to address this comment, with emphasis on the impact of exacerbations. The importance of exercise impairment is already addressed in the discussion, and given that this result was confounded to a degree by FEV1, we would not wish to overemphasise this latter finding.

5. There is no comparison with the studies available in the literature of worse prognosis in patients with COPD and anemia.

Our aim was to separate the effects of iron deficiency per se from those of anaemia, and we were able to demonstrate that there is no difference in haemoglobin between our cohort patients with ID and those who are IR. However, the reviewer quite rightly highlights the fact that anaemia does confer a worse prognosis in its own right in COPD, and we have now made this clear in the discussion, with a number of further references.

Additional revisions

Whilst this manuscript was under review, two reports were published in non-COPD populations (PMIDs 25689633 and 25176939), which provide further clinical evidence of the role of iron in cardiopulmonary disease. We believe these enhance the general interest level in our own work, and reference to both has accordingly been made at appropriate points in the manuscript. We hope this will meet with the approval of the reviewers and the Editor.