ORIGINAL ARTICLE

IRON DEFICIENCY WITHOUT ANAEMIA IN COPD PATIENTS: ASSESSING EXERCISE CAPACITY AND EXACERBATION FREQUENCY

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Background: Chronic Obstructive Pulmonary Disease (COPD) is a global health challenge with significant morbidity and mortality. Iron deficiency, including non-anaemic iron deficiency (NAID), has been identified as a potential comorbid in COPD, affecting patient outcomes and disease severity. This study aimed to investigate the prevalence and impact of iron deficiency on the severity and clinical outcomes in COPD patients. **Methods:** In this descriptive cross-sectional study, 289 individuals diagnosed with COPD were enrolled and underwent comprehensive medical assessments, including haematological tests and spirometry from December 2019 to December 2023. The study focused on measuring iron levels, exercise capacity, and exacerbation frequency, comparing iron-deficient and non-iron-deficient groups. **Results:** The study found that 46.7% of participants had iron deficiency. Those with iron deficiency showed significantly lower exercise capacity as measured by the six-minute walk distance and experienced a higher frequency of yearly COPD exacerbations. However, no significant differences were observed in airflow limitation and the overall quality of life between the iron-deficient and non-iron-deficient groups. **Conclusion:** The findings suggest that iron deficiency, particularly NAID, is associated with a more severe progression of COPD, characterized by reduced exercise capacity and increased exacerbation frequency. These results highlight the importance of considering iron deficiency in the management of COPD to potentially improve patient outcomes. **Keywords:** Chronic Obstructive Pulmonary Disease (COPD); Iron Deficiency; Non-Anaemic Iron Deficiency (NAID); COPD Exacerbations; Exercise Capacity in COPD; COPD Management Strategies

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) poses a significant global health burden, as evidenced by its high morbidity and mortality rates.[1] The prevalence of COPD and asthma in lower and middle-income countries remains under-recognized due to diagnostic challenges.[2] A recent comprehensive review highlights that these conditions account for over 80% of respiratory-related deaths in such regions.[3] In South Asia, for instance, COPD and asthma are responsible for 8% of Disability-Adjusted Life Years, indicating a critical need for improved awareness and diagnostic capabilities in these areas.[4,5] In Pakistan, the prevalence of COPD and asthma is estimated at 2.1% and 4.3%, respectively.6 The progression and impact of COPD are exacerbated by various associated health conditions, which increase its morbidity, economic burden, and mortality. Common comorbidities include cardiovascular diseases, diabetes, pneumonia, weight loss, and anaemia, each adversely affecting COPD patients.[7] Therefore, it is vital to identify and manage these comorbid conditions in the treatment of COPD.

Iron plays a crucial role in several metabolic processes, including DNA synthesis, oxygen transport, cellular function, and mitochondrial energy production.[8] However, environmental iron and particulate matter can disrupt lung iron homeostasis.[9–11] Genetic factors related to iron metabolism are implicated in COPD, and exposure to tobacco smoke, pollution, and other harmful agents may modify these genetic pathways, potentially leading to COPD.[12–15] Inflammatory cytokines in COPD can also affect iron regulation, resulting in increased iron absorption and storage in the reticuloendothelial system.[16,17] Iron deficiency features commonly in chronic diseases such as pulmonary arterial hypertension (PAH), and chronic heart failure (CHF) even in the absence of anaemia.[18–20] Iron deficiency is also prevalent in

various chronic conditions, including chronic kidney disease, rheumatoid arthritis, Parkinson's disease, and inflammatory bowel disease, irrespective of the presence of anaemia associated with iron deficiency.[20]

The prevalence of anaemia in COPD patients varies widely according to different studies, influenced by factors such as study design, patient demographics, regional differences, and varying definitions of anaemia.[21] There is a pressing need for standardized research to determine the exact prevalence of anaemia in COPD patients. John and colleagues have also explored the frequency of anaemia in patients hospitalized with various chronic conditions.[22] In comparison, diseases like heart failure, rheumatoid arthritis, and cancer have been more extensively researched about anaemia.

Anaemia prevalence in COPD ranges from 7.5–33%, with John *et al*. reporting a 13% incidence in a study of 101 COPD patients, suggesting inflammation as a contributing factor.[22] Anaemia observed was typically normocytic and normochromic. John and colleagues found significantly higher levels of inflammatory markers in anaemic COPD patients compared to controls, particularly interleukin-6 (IL-6) and C-reactive protein (CRP).22 Halpern and colleagues identified a 21% prevalence of anaemia among COPD patients in a US Medicare claims study.[23] Parveen et al. reported an 18% incidence in a hospital-based cross-sectional study, while Shorr et al. found a 33% prevalence of anaemia in a retrospective analysis of COPD patients in the USA.[24,25] These findings contrast with the traditional focus on polycythaemia in COPD as emphasized in the medical literature.

The overall prevalence of anaemia in COPD patients was 23.1%, similar to 23.3% in chronic heart failure patients. Anaemia was most common in patients with renal insufficiency and cancer, with prevalences of 71.8% and 45%, respectively.26 In Pakistan, anaemia prevalence in COPD patients varied from 24–45%, depending on the study.27-29 The link between iron deficiency and COPD severity, particularly non-anaemic iron deficiency (NAID), remains under-researched, especially in certain regions. This study seeks to explore the prevalence of iron deficiency, both anaemic as well as non-anaemic iron deficiency in COPD patients and to correlate the severity of the iron deficiency severity of COPD.

MATERIAL AND METHODS

In this descriptive cross-sectional study, 289 individuals diagnosed with Chronic Obstructive Pulmonary Disease (COPD) were enrolled, on the pulmonology OPD clinic of BBS Teaching Hospital, Abbottabad, following the guidelines of the Global Initiative for Chronic Obstructive Lung Disease from December 2019 to December 2023.[30,31] Eligibility criteria included no recent exacerbations or hospital admissions within the past four weeks and normal haemoglobin levels, as defined by the World Health Organization (haemoglobin levels above 13 g/dl and 12 g/dl for males and females, respectively). Exclusion criteria encompassed pregnancy, lactation, ongoing anaemia treatment, potential blood loss, and the presence of malignancies.

Participants underwent comprehensive medical and physical assessments by a qualified pulmonologist. The evaluations consisted of haematological tests and spirometry. The haematological tests included: i) Iron studies, where serum iron and total iron-binding capacity (TIBC) were measured using the ferrozine method, and serum ferritin levels were determined through chemiluminescence; ii) Pulmonary function tests were conducted using the Benchmark model lung function machine (Spirodoc® II, MIR.), applying specific prediction equations for Pakistani population.32 Essential measurements included Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC), and the FEV1/FVC ratio; iii) A six-minute walk test conducted by the American Thoracic Society guidelines[33]; iv) The Urdu version of the COPD Assessment Test (CAT).[34]

The COPD Assessment Tool (CAT) is a patient-reported outcome measure (PRO) that consists of 8 items in four domains: cough, phlegm, chest tightness, and breathlessness. It is a quick and easy tool to complete, taking only 2–3 minutes, and it has a scoring range of 0–40, with higher scores reflecting worse health status. The CAT is designed for COPD patients and has been assessed and validated in various languages and settings. The CAT is primarily used as a clinical tool and has demonstrated a good correlation with other indicators of disease severity and exacerbation risk.

For this study, the serum ferritin cutoff value was set at 30 ng/ml, exceeding the WHO recommendation of 15 mcg/l, to identify iron deficiency. This was based on recent findings that suggest a 30 ng/ml threshold results in an enhanced sensitivity of 92% with an 83% positive predictive value, addressing the limitations of lower ferritin levels in accurately detecting iron deficiency.[35,36] The study also acknowledged ferritin as an acute phase reactant that could lead to unreliable readings.[36,37] The criteria for non-anaemic iron deficiency were ferritin levels lower than 30 ng/ml or transferrin saturation below 20%.[35] The sample size was determined using the following statistical formula, ensuring the estimated population

proportion fell within the desired margin of error at a specified confidence level:

$$n = \frac{z^2_{1-\frac{\alpha}{2}} \cdot P \cdot (1-P)}{d^2}$$

where:
- n is the sample size,
- $z^2_{1-\frac{\alpha}{2}}$ is the z-score corresponding to the desired confidence level,
- P is the expected population proportion,
- d is the absolute precision or margin of error.

A 95% confidence level (alpha of 5%), an anticipated population proportion (P) of 24% of iron deficiency in COPD patients[27], and an absolute precision (d) of 0.05 were chosen for this study. These parameters led to a calculated sample size of 289, considered adequate to estimate the population proportion with the required precision and confidence. Participants were recruited through consecutive non-probability sampling.

RESULTS

In this study, 289 subjects were examined, consisting of 192 males and 97 females, reflecting a male predominance in the participant demographic. The study population was split into two groups for data analysis: COPD patients with no iron deficiency and COPD patients with non-anaemic iron deficiency (NAID). The mean age of the participants was determined to be 59.1±6.12 years. Within this cohort, 135 participants (46.7%; 95% CI, 35.1–59.2%) were found to have iron deficiency.

An age difference was noted between both groups with NAID and the COPD patients who didn't have iron deficiency, with the average ages being 61.2 years and 56.1 years, respectively. Despite similarities in baseline characteristics such as smoking status, body mass index, weight, and height, age was a distinguishing factor. The group with non-anaemic iron deficiency exhibited significantly lower levels of serum iron, transferrin saturation, and serum ferritin, along with an increased total iron binding capacity. Haemoglobin concentrations in the cohort varied between 12–17 g/dl, with the NAID group demonstrating significantly lower levels. A median value of 59 mcg/l (IQR: 43–93; range 8-265 mcg/l) was observed for serum ferritin levels. Lower levels of haematocrit (41.21±3.82 vs 46.21±2.98; *p*=0.003) and haemoglobin (12.18±0.82 mg/dl; vs 14.68±1.18; *p*=0.003) were associated with iron deficiency among the participants. However, no significant differences were found in MCHC, MCV, and white blood cell counts between participants with or without iron deficiency, who had COPD.

Further analysis of the impact of iron deficiency revealed a marked difference in the six-minute walk distance (6MWD) between groups. Those with NAID averaged 358.17±91.5 meters, in contrast to 441.6±68.12 meters in those who didn't have NAID (*p*=0.001). The iron deficiency group also experienced a higher frequency of yearly COPD exacerbations (*p*=0.003), with a larger proportion facing at least two exacerbations annually (*p*=0.001). No significant differences were observed in resting pO2, SaO2, and SpO2 levels between the two groups (*p* values of 0.11 and 0.31).

Most of the participants (82%) were categorized as having moderate to severe airflow limitation (GOLD 2 and 3), with 11% in the very severe category (GOLD 4) and 7% in the mild category (GOLD 1). The distribution across these various categories of airflow limitation did not show significant variation between groups. Additionally, no significant differences were noted in Forced Vital Capacity (FVC) as a percentage of predicted value [83.41% (17.43) vs 84.97% (18.79), *p*=0.87] and Forced Expiratory Volume in one second (FEV1) as a percentage of predicted value [53.41% (18.72) vs 47.61% (15.5), *p*=0.14] when comparing non-anaemic iron deficient (NAID) and the normal (no iron deficiency) groups of study participants.

The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) scores were lower in the NAID group, though this difference was not statistically significant (18.22±6.34 vs 21±7.50; *p*=0.06). In the NAID group, the distribution among GOLD groups A, B, and D was 5.6%, 30.6%, and 63.9% respectively, in contrast to 18.6%, 58.1%, and 23.3% in the normal (no iron deficiency) group. This delineates a notable disparity in the prevalence of patients in the GOLD D category between the NAID and no iron deficiency groups, with a significant concentration in the former (63.9% vs 23.3% based on the GOLD 2019 criteria, *p*<0.001).

DISCUSSION

This study focused on exploring iron deficiency in COPD patients, especially those without apparent anaemia, a topic that has not been extensively researched. The findings of this study reveal a high rate of iron deficiency without anaemia among patients with COPD. These individuals demonstrated diminished functional capabilities, as indicated by reduced 6-MWD, a history of frequent exacerbations in the past year, and a more severe grading according to the GOLD COPD assessment. Nevertheless, this study did not find notable differences in the degree of airway obstruction, or the life satisfaction of patients with iron deficiency or patients without iron deficiency.

An interesting observation was the lower haemoglobin levels in the iron-deficient (ID) group compared to the non-iron-deficient (NID) group,

despite all participants being classified as non-anaemic based on WHO criteria. This finding suggests potential disruptions in erythropoiesis and raises the possibility of these patients developing overt anaemia over time. Additionally, the ID group exhibited lower haematocrit levels, which Chambellan *et al*. have identified as a critical predictor of mortality; they reported a 14% decrease in relative risk of death for every 5% increase in haematocrit, ranking it as a prominent mortality predictor next to age.[38]

Concerning exercise capacity, the ID group had a significantly reduced 6-minute walk distance (6MWD). The choice of the 6-minute walk test (6MWT) was based on its relevance to everyday activities, which are typically performed at submaximal exertion levels, making the 6MWD a more accurate reflection of patients' functional exercise capacity.39 Iron status affects both tissue oxidative and oxygen-carrying capacities, which influence exercise capacity. Iron deficiency reduces tissue oxidative capacity, which affects endurance and exertion levels, in proportion to its severity. However, only severe iron deficiency, which also significantly affects erythropoiesis, impacts oxygen-carrying capacity.40 These results are consistent with previous studies that have associated iron deficiency, with or without anaemia, with impaired exercise capacity in COPD patients.[41,42]

The cohort under study showed that patients who had iron deficiency (NAID) had more acute exacerbations in the previous year than those who did not have iron deficiency (NID). Acute exacerbations play a key role in the worsening and pathogenesis of COPD and are a key indicator of patient outcomes. The risk of having future exacerbations is mainly determined by the history of previous exacerbations, which also affect the disease prognosis significantly.[43,44] This strong association between iron deficiency and the number of acute exacerbations underscores its possible importance in COPD management and highlights the need for preventing exacerbations as a core component of COPD treatment.

The findings of this study are consistent with those of previous studies that reported a high prevalence of NAID (non-anaemic iron deficiency) in chronic diseases, such as heart failure and pulmonary hypertension.[45,46] Likewise, some studies that focused on COPD have found comparable results.[42,47] However, the definition of iron deficiency in COPD patients is ambiguous. Some studies have applied more rigorous criteria[47], while others have used conventional indicators, such as a ferritin level below 100 mcg/L, which are also common in heart failure and pulmonary hypertension research.[42,48] In this study, we selected a threshold of ferritin under 30 mcg/L or transferrin saturation below 20% to enhance sensitivity, but we acknowledge that these parameters are not well-validated in this context.[37]

Our study reveals that iron deficiency is linked to more frequent and severe episodes and reduced ability to perform daily activities in patients with COPD. A possible intervention is iron supplementation, which has shown positive effects on the functional capacity of patients with heart failure and pulmonary hypertension. This could be a promising strategy for COPD treatment, even though there is still a need for more reliable and conclusive evidence on the benefits of iron supplementation for heart failure.[48] Therefore, we suggest that COPD patients should be evaluated for iron deficiency and considered for iron supplementation.

CONCLUSION

In conclusion, this study indicates that iron deficiency correlates with a more severe manifestation of Chronic Obstructive Pulmonary Disease (COPD), diminished exercise capacity, and a higher frequency of exacerbations annually compared to patients without iron deficiency. However, we observed no notable differences in airflow limitation and overall quality of life between the two groups. Consequently, our findings imply that non-anaemic iron deficiency (NAID) is linked to a more severe progression of COPD and an increased likelihood of exacerbations, which may lead to a worse prognosis. Therefore, NAID should be carefully considered in the management of COPD.

Strengths and Limitations:

This research aimed to explore the association between iron deficiency and COPD in our region. The study compared the clinical outcomes, quality of life, and functional status of patients with and without iron deficiency. The results showed that iron deficiency could be a marker of a worse prognosis in COPD patients.

However, this study had some limitations that need to be addressed:

The study was conducted in a secondary care hospital, where most of the patients had acute COPD exacerbations or moderate to severe COPD. This may not reflect the wider population.

Also, the sample size was relatively small, which reduced the generalizability of the findings and called for more studies with larger samples to confirm these results.

This study was also limited by its single-centre design, which may not represent the implications for all COPD or asthma patients.

The lack of a non-COPD control group prevented us from comparing the prevalence of iron

deficiency in non-anaemic COPD patients with that in the general population.

Furthermore, this study did not measure C-reactive protein levels and their possible relation to iron deficiency. Despite these limitations, this study added to the knowledge of COPD, by emphasizing a significant, potentially treatable comorbidity that has been mostly ignored.

Another limitation of this study based on a single centre was the absence of a comparison of symptoms and signs of COPD between those with non-anaemic iron deficiency and those with iron deficiency anaemia, but this comparison was beyond the scope of our study design.

We recommend future studies with larger cohorts further to investigate the role of iron deficiency in COPD and evaluate the potential advantages of iron supplementation in this setting.

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AUTHORS' CONTRIBUTION

MAA: Literature search, the conceptualization of the study design, data collection, data analysis, and write-up. AN, SAQ, NH, NK, MAR: Data interpretation, proofreading.

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