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Assessment of trace elements, systemic inflammation, and electrolytes in patients with chronic obstructive pulmonary disease

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Abstract

Background Systemic inflammation, electrolytes, and trace element derangements are thought to be involved, directly or indirectly, in chronic obstructive pulmonary diseases (COPD).

Aim Our aim is to evaluate systemic inflammation and disturbance in serum electrolytes and trace elements in patients with COPD.

Methods This study was conducted in the Chest Department, Cardiothoracic Minia University Hospital. One hundred COPD patients and 40 healthy controls were included in the study. Sixty patients were in a stable state, while 40 patients were in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Serum C-reactive protein (CRP), TNF-α, copper (Cu), zinc (Z), Na, K, and Mg levels were measured for all participants.

Results CRP, TNF, Cu, and Z were significantly higher in the stable group than in the control group (p-value 0.0002*, 0.0018*, 0.04*, 0.034*, respectively) with significantly higher levels during exacerbation (8.47 ± 6.3, 24.36 ± 9.53, 201 ± 39.02, 192 ± 32.3). The Cu/Z ratio was significantly lower in the exacerbation group than in the stable group (p-value 0.042*). Serum levels of Na, K, and Mg were significantly lower in the patients group than in the control group (p-value 0.024*, 0.039*, 0.044*, respectively), with more reduction observed in the exacerbation group (132 ± 5.45, 3.24 ± 0.52, 1.67 ± 0.38).

Conclusion CRP, TNF-α, Cu, and Z levels were significantly higher in stable COPD patients, with higher levels during exacerbation. The Cu/Z ratio was lower in the exacerbation group than in the stable group. Na, K, and Mg levels were lower in patients than in the control group with more reduction during exacerbation.

Keywords COPD, Biomarkers, Trace elements, Electrolytes

Introduction

COPD is one of the most common causes of health problems worldwide. It is a disease that is associated with several systemic features that affect its morbidity and mortality [1, 2].

The most prominent features of COPD are systemic inflammation and oxidative stress. There is a growing interest in establishing the significance of systemic inflammatory biomarkers in COPD patients, as they could be useful in evaluating exacerbations, monitoring disease progression, and evaluating treatment outcomes [3].

C-reactive protein (CRP) is a biomarker for systemic inflammation, produced mostly by hepatocytes in response to tissue injury or inflammation [4].

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Tumor necrosis factor-alpha (TNF-α) is a key modulator of the immune system's response to infection. At sites of inflammation, this cytokine regulates the function of polymorphs and lymphocytes, with essentially protective benefits for the host. Increased TNF-α production may enhance an injury process locally, and also, elevated circulating levels may have negative systemic consequences [5].

Trace elements are hypothesized to play a role in the pathogenesis of many diseases, either directly or indirectly. Trace elements play an important function in the inhibition and activation of enzyme processes [6]. Zinc, for example, is a cofactor for various enzymes and is important for cell membrane stability, protein synthesis, proper tissue growth, and nucleic acid metabolism [7]. Severity of COPD exacerbation is associated with increased levels of copper (Cu) and zinc (Zn) [8].

Patients with COPD are liable for various electrolyte derangements, especially during exacerbations. Hyponatremia is typically observed in the final stages of COPD. Hypokalemia may also occur independently or concomitantly with hyponatremia, and because magnesium plays a role in muscle tone, a drop in magnesium levels in COPD is a component that reduces respiratory muscle function and causes muscle fatigue [9].

Aim
The study aims to assess the level of CRP, TNF-α, copper, zinc, Na, and K in patients with stable COPD and AECOPD. Also, it aims to determine the relation between these elements and the need for non-invasive ventilation (NIV) and its success.

Patients and methods
The study was a cross-sectional observational study. It included all COPD patients who were presented as outpatients to the chest clinic or admitted to the inpatient ward or respiratory ICU at Cardiothoracic Minia University hospital during the period between June and December 2019.

Patients with cardiovascular diseases, diabetes mellitus, chronic kidney disease, chronic liver disease, collagen vascular diseases, cancer, currently smoking, current pneumonia, or inflammation or refused to participate in the study were excluded.

Forty matched controls with normal lung function were included in the study.

The included patients were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition [1].

The diagnosis of exacerbation was based exclusively on the clinical presentation of the patient, who complained of an acute change in dyspnea, cough, and/or sputum production that was beyond the normal day-to-day variation [1].

Clinical and demographic data were recorded at the time of presentation, including age, sex, smoking status, biomass fuel exposure, occupation (current and previous), and frequency of COPD exacerbation, in addition to the assessment of chest symptoms like cough, expectoration, dyspnea, and its grade by mMRC.

Complete general and local chest examinations were performed on all patients and controls. Spirometry was done for non-previously diagnosed patients using (SensorMedics, USA) to confirm COPD diagnosis based on a post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio of less than 0.70 [1].

Laboratory investigations were done for all patients and controls, including complete blood count, liver, renal function tests, and assessment of serum levels of sodium, potassium, and magnesium.

For the assessment of CRP, TNF-α, zinc, copper, and magnesium, about 8 ml of venous blood was drawn by sterile venipuncture. The serum was separated from blood cells by centrifugation, then stored at -20 °C until analysis.

TNF-α was measured by enzyme immune assay (EIA) (bioassay technology laboratory, Jiaxing, China) (Engelberts et al.) [10]. The calibration graphs were constructed applying normal aqueous standards. Serum level determination of Zn, Cu, and Mg had been carried out using the colorimetric method (BioDiagnostic, Giza, Egypt). Finally, CRP was measured by a quantitative turbidimetric method (SPINREACT, Girona, Spain).

Ethical considerations
The nature of the present study was explained to all patients. Laboratory procedures represented standard care and posed no ethical conflicts. Verbal consent was obtained from all patients. The study was approved by the research ethics committee of the Minia Faculty of Medicine.

Statistical analysis
Analyses were carried out with IBM SPSS statistics (version 17; SPSS for Windows; SPPS Inc., Chicago, IL, USA). Statistical significance was set at a *p*-value less than 0.05.

Results
One hundred COPD patients (60 stable and 40 AECOPD) and 40 controls were included in this study. Twenty-five of those with exacerbation were admitted to the internal ward of the chest department, while 15 of them were admitted to the respiratory ICU due to the need for (NIV).

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Table 1 Comparison between stable COPD patients and controls regarding laboratory data

	Stable COPD patients, N = 60	Healthy controls, N = 40	p
CRP (mg/dL), mean ± SD	4.06 ± 2.23	1.73 ± 1.25	0.0002*
TNF-α (pg/mL), mean ± SD	19.8 ± 7.47	11.07 ± 3.30	0.0018
Copper (mg/dL), mean ± SD	162 ± 34.63	120 ± 27.65	0.04*
Zinc (mg/dL), mean ± SD	140 ± 45	100 ± 24.2	0.034*
Cu/Z ratio, mean ± SD	1.18 ± 0.2	1.23 ± 0.12	0.4
Na (mmol/L), mean ± SD	139 ± 5.03	142.3 ± 2.05	0.024*
K (mmol/L), mean ± SD	3.96 ± 0.52	4.34 ± 0.24	0.039*
Mg (mmol/L), mean ± SD	2.7 ± 1.52	3.64 ± 1.45	0.044*

N number, *SD* standard deviation, *CRP* C-reactive protein, *TNF* tumor necrosis factor, *Cu/Z* copper/zinc ratio, *Na* sodium, *K* potassium, *Mg* magnesium

*P <0.05 significant

Laboratory data of stable COPD patients and controls were shown in Table 1, which revealed a significantly higher CRP level in patients than in the control group with p 0.0002. Also, TNF-α was significantly higher in the patient group vs in controls (p 0.0018).

Regarding trace elements, copper and zinc were significantly higher in stable patients than in the control group (p 0.04 and 0.034, respectively). The Cu/Z ratio was insignificantly lower in the stable group (p 0.4).

Serum Na, K, and Mg were significantly lower in the stable COPD patients' group than in the control group with all p-values < 0.05.

Table 2 shows the differences between stable COPD patients and those during an exacerbation, regarding laboratory measures. It elucidated a significant difference between both groups regarding CRP level, which was higher during exacerbation (8.47 ± 6.3 versus 4.06 ± 2.23 mg/L) in the stable group ($p < 0.001$). TNF-α level was higher in the exacerbation group vs in the stable group (p 0.0001).

Regarding trace elements, copper and zinc were significantly higher in the exacerbation group than in

the stable group (p 0.041 and 0.01, respectively). The Cu/Z ratio was significantly higher in the stable group (p 0.042).

Serum Na, K, and Mg were significantly lower in the AECOPD patients group than in the stable COPD group, with p (0.021, 0.01, and 0.001, respectively).

Comparing laboratory parameters in patients who required NIV and those that did not require it (Table 3) elucidated insignificantly higher CRP level in NIV-ve patients (p 0.323), while TNF-α was higher in the NIV + ve group, but also insignificantly (p 0.51).

Insignificant differences between both groups were found regarding Cu, Z, and Cu/Z ratio (p 0.64, 0.58, and 0.21, respectively).

Serum Na and K levels were found to be lower in the NIV-ve group than in the NIV + ve group, but to nonsignificant values (p 0.67 and 0.32, respectively). Mg level was insignificantly lower in the NIV + ve group (1.65 ± 0.32) than in the NIV-ve group (1.68 ± 0.22) (p 0.42).

As shown in Table 4, 9 of the patients who were put on NIV had been weaned successfully, while 6 patients required invasive MV due to failure of NIV.

CRP and TNF-α levels were insignificantly higher in the NIV failure group (p 0.323 and 0.19, respectively). Also, insignificant differences between both groups were found regarding Cu, Z, and Cu/Z ratio (p 0.39, 0.38, and 0.45, respectively).

Discussion

In this study, CRP and TNF-α levels were compared between healthy subjects and those with stable COPD, and also between stable COPD patients and those with AECOPD. The study revealed that there were significantly higher CRP and TNF-α levels in stable COPD patients than in the control group. This agrees with the systemic review and meta-analysis conducted by Gan et al. [11] that concluded that compared to healthy controls, individuals with COPD had significantly raised

Table 2 Comparison between stable COPD and AECOPD patients

	Stable COPD, N = 60	AECOPD, N = 40	p
CRP (mg/dL), mean ± SD	4.06 ± 2.23	8.47 ± 6.3	< 0.001*
TNF-α (pg/mL), mean ± SD	12.34 ± 6.33	24.36 ± 9.53	0.0001*
Copper (mg/dL), mean ± SD	162 ± 34.63	201 ± 39.02	0.041*
Zinc (mg/dL), mean ± SD	140 ± 45	192 ± 32.3	0.01*
Cu/Z ratio, mean ± SD	1.18 ± 0.2	1.02 ± 0.3	0.042*
Na (mmol/L), mean ± SD	139 ± 5.03	132 ± 5.45	0.021*
K (mmol/L), mean ± SD	3.96 ± 0.52	3.24 ± 0.52	0.01*
Mg (mmol/L), mean ± SD	2.7 ± 1.52	1.67 ± 0.38	0.001*

N number, *SD* standard deviation, *CRP* C-reactive protein, *TNF* tumor necrosis factor, *Cu/Z* copper/zinc ratio, *Na* sodium, *K* potassium, *Mg* magnesium

*P <0.05 significant

Table 3 Laboratory data in patients on NIV and non-NIV patients

	NIV + ve, N = 15	NIV-ve, N = 25	P
CRP (mg/dL), mean ± SD	8.59 ± 4.7	8.7 ± 6.3	0.323
TNF-α (pg/mL), mean ± SD	23.95 ± 10.5	21.1 ± 9.13	0.51
Copper (mg/dL), mean ± SD	196 ± 32	200 ± 37.3	0.64
Zinc (mg/dL), mean ± SD	190 ± 38	188 ± 35.4	0.58
Cu/Z ratio, mean ± SD	1.03 ± 0.3	1.06 ± 0.2	0.21
Na (mmol/L), mean ± SD	133 ± 4.08	132 ± 2.06	0.67
K (mmol/L), mean ± SD	3.25 ± 0.64	3.23 ± 0.53	0.32
Mg (mmol/L), mean ± SD	1.65 ± 0.32	1.68 ± 0.22	0.42

N number, *SD* standard deviation, *CRP* C-reactive protein, *TNF* tumor necrosis factor, *Cu/Z* copper/zinc ratio, *Na* sodium, *K* potassium, *Mg* magnesium, *NIV* non-invasive ventilation

CRP and TNF levels, indicating the presence of persistent systemic inflammation in COPD. Moreover, the results of El-Deek et al. [12] and Firouzjahi et al. [13] revealed significantly higher hs-CRP in COPD patients. Abdelsadek et al. [14] noticed that COPD patients had higher CRP levels than normal controls (smokers and non-smokers), and the difference was statistically significant (p 0.05). Also, the level of CRP was proportionally related to the stage of the disease, as the level of CRP increased significantly as the severity of COPD increased. Similarly, Karadag et al. [15] investigated 35 male patients with stable COPD and 30 age and sex-matched subjects with normal pulmonary functions. Serum CRP was significantly higher in stable COPD patients than in control subjects ($p < 0.001$).

Broekhuizen et al. [16] found that 47% of 102 COPD patients had raised CRP levels. This also agrees with Sin and Man [17], as they found higher circulating levels of CRP in participants with airflow obstruction than in those without airflow obstruction. Also, Schols et al. [5] found significantly higher CRP levels in COPD patients than in controls.

Table 4 Laboratory measures among NIV success and failure groups

	NIV success, N = 9	NIV failure, N = 6	P
CRP (mg/dL), mean ± SD	8.3 ± 4.7	9.08 ± 2.1	0.323
TNF-α (pg/mL), mean ± SD	22.97 ± 10.85	27.2 ± 8.01	0.19
Copper (mg/dL), mean ± SD	185 ± 31	203 ± 28.2	0.39
Z (mg/dL), mean ± SD	191 ± 35	205 ± 16.6	0.38
Cu/Z, mean ± SD	0.97 ± 0.13	0.99 ± 0.25	0.45
Na (mmol/L), mean ± SD	133.24 ± 3.6	132 ± 5.3	0.46
K (mmol/L), mean ± SD	3.27 ± 0.84	3.25 ± 0.64	0.39
Mg (mmol/L), mean ± SD	1.64 ± 0.29	1.66 ± 0.32	0.45

N number, *SD* standard deviation, *CRP* C-reactive protein, *TNF* tumor necrosis factor, *Cu/Z* copper/zinc ratio, *Na* sodium, *K* potassium, *Mg* magnesium, *NIV* non-invasive ventilation

The current study elucidated significantly higher CRP levels in patients who presented with AECOPD than in patients with stable COPD. Moreover, there were higher levels in the patient group who received NIV and in those who failed the NIV than in those who succeeded in the trial; however, this was of no statistical significance. This agrees with Valipour et al., [18] as they revealed in their study that CRP level was higher in AECOPD than in stable COPD.

CRP assessments provide additional prognostic information beyond those provided by traditional prognostic indicators in patients with mild to moderate COPD, according to Man et al. [19], and may enable more accurate detection of patients at a high risk of mortality. Moreover, de Torres et al., [20] concluded that there was a strong inverse relationship between the rise in CRP level in COPD and the PaO$_2$ and 6MWT.

Cano et al. [21] documented that CRP predicts mortality in patients with chronic respiratory failure. The inconclusive results in the current study, regarding the relationship between CRP level and the need for or success of NIV, may be due to the small number of patients in these groups.

Regarding TNF-α, the results of Calikoglu et al. [22] also matched with the current study results, as their results showed that TNF-α levels were higher in stable patients than in controls; however, the difference is statistically insignificant, and this may be related to increased inflammation in patients. They also found that TNF-α level was significantly higher in patients experiencing exacerbation than in stable patients. Von Heahling et al. [23] observed a significant correlation between serum TNF levels and disease severity, as measured by FEV1 percent predicted ($r = 0.49$, $p = 0.02$) and that spontaneous TNF-α production was 5.0 times higher in severe COPD patients compared to mild-to-moderate COPD patients ($p = 0.02$).

Trace elements are needed in very small amounts as important components of antioxidant enzymes, like superoxide dismutase and catalase (Karadag et al.) [24]. It is fair to expect that trace elements will have an effect on the COPD process, either directly or indirectly (El-Attar et al.) [25].

The current study showed significantly higher Cu and zinc levels in the stable COPD patients than in controls, and significantly higher levels in the AECOPD group than in the stable group, with a significantly lower Cu/Z ratio in the AECOPD group. Similar to these results, Tanrikulu et al. [8] found that serum Cu and Zn levels during the attack period of patients with COPD were increased, and Cu/Zn ratio decreased. Isik et al. [26] also reported that the Cu level was higher in COPD patients than in control.

Pearson et al., [27] observed a statistically significant inverse relationship between FEV1 and plasma copper in their investigation. Their findings are congruent with those of the Second National Health and Nutrition Survey, which found a 50% rise in bronchitis and wheeze symptoms for every 2 SD increase in serum copper (Schwartz & Weiss) [28].

According to Gray et al. [29] sputum Zn and Cu levels were greater in suppurative and inflammatory lung illnesses, and Zn levels decreased following treatment for suppurative and inflammatory lung diseases. Increased Cu and Zn levels have been associated with disease-related inflammation (Tanrikulu et al.) [8].

Isik et al. [26] reported that there were no differences in zinc (Zn) concentration and Cu/Zn ratio between COPD patients and the control group. Kırkıla et al. [30] studied thirty patients with COPD and 15 healthy non-smokers who were matched for age and sex. Zinc level was lower in the patients compared to the controls. Agin and Namavary [31] found that hypozincemia and hypocupremia were found in 11% and 14%, respectively. The disagreement between these results with the current results can be attributed to the differences in the severity of disease or other comorbid conditions.

In the final stages of COPD, hyponatremia is common, and this could be due to chronic hypoxia and hypercapnia, renal failure, or heart failure. Also, the use of diuretics, bronchodilators, or steroids, malnutrition and low intake during acute exacerbations could be implicated in the prevalence of hyponatremia in COPD patients. Hyponatremia can be caused by activation of the renin–angiotensin–aldosterone pathway and abnormally increased plasma arginine vasopressin (AVP) in COPD (Adiody et al.) [9].

Hyponatremia, regardless of the underlying cause, may be a predictor of poor COPD patient outcomes, including death (Suri et al. [32] and Porcel et al. [33]).

Hypokalemia can occur alone or in conjunction with hyponatremia (Adiody et al. [9]). COPD patients with acute respiratory failure, who also had hypokalemia, had a greater mortality rate (Hussain et al.) [34].

In accordance with these literatures, the current study revealed significantly lower Na, K, and Mg levels in the stable COPD patient group than in the control group and significantly lower levels during exacerbation than in the stable condition.

Adiody et al. [9] reported that dyselectrolytemia was more severe in AECOPD compared with stable COPD, with significantly lower Na, K, and Mg levels in the AECOPD group. They also found hyponatremia in 28% of stable COPD patients, and 77% of the AECOPD group required NIV, hypokalemia in 69%, and hypomagnesemia in 62% of the exacerbation group requiring NIV

indicating that when there was associated dyselectrolytemia, which led to muscle weakness, disorientation, and possibly increase the need for NIV.

Das et al. [35] found significantly lower Na and K levels in the AECOPD group than in the control group. Moreover, Ur Rashid [36] found low Na and K levels in patients with AECOPD (131 ± 5.66 and 3.20 ± 0.44, respectively).

The small number of patients is a major limitation of the current study.

CRP, TNF, Cu, and Z levels were significantly higher in COPD patients in comparison with controls, with higher levels during exacerbation. A lower Cu/Z ratio in the exacerbation group than in the stable group was observed in the current study. Na, K, and Mg levels were lower in patients than in the controls, with lower levels during the exacerbation group than in the stable group. Insignificant differences were found between the group of patients who required NIV and those treated without NIV, and between those who succeeded in the NIV trial and those who failed the trial.

Abbreviations

CRP	C-reactive protein
COPD	Chronic obstructive pulmonary disease
TNF-α	Tumor necrosis factor-alpha
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ABGs	Arterial blood gases
Na	Sodium
K	Potassium
Mg	Magnesium
Cu	Copper
Z	Zinc
ICU	Intensive care unit
SD	Standard deviation
NIV	Non-invasive ventilation
PaO$_2$	Arterial blood oxygen tension
6MWT	6-Min walking test
hsCRP	High-sensitivity C-reactive protein

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Minia University, Faculty of Medicine, ethical approval no.: 369–9-2022. The subject participant provided written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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