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Evaluation of trace element levels in patients diagnosed with pulmonary embolism

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Abstract

The aim of this study is to determine the serum levels of essential trace elements such as zinc, copper, magnesium, and iron in patients diagnosed with pulmonary embolism, and to evaluate relationship between these trace element levels and pulmonary embolism. A total of 52 patients were included in the study: 26 patients diagnosed with pulmonary embolism (Group I) and 26 completely healthy individuals (Group II). Serum zinc, copper, iron, and magnesium levels were assessed. Magnesium and iron levels were measured using colorimetric methods, while zinc and copper levels were measured using atomic absorption spectrometry. No significant difference was found between the groups in terms of age. Copper levels in Group I were statistically significantly higher than in Group II. Levels of zinc, iron, and magnesium in Group I were statistically significantly lower than in Group II. Zinc, copper, iron, and magnesium levels show significant alterations in pulmonary embolism and may be associated with its clinical status. These trace elements have the potential to be evaluated as biomarkers for the diagnosis and follow-up of the disease, although their exact role in the pathogenesis requires further investigation.

Keywords: Pulmonary embolism, zinc, copper, magnesium, iron

Introduction

Pulmonary embolism (PE) is a sudden-onset disease characterized by cardiovascular decompensation, characterized by chest pain, shortness of breath, cough, tachycardia, hemoptysis, tachypnea, and fear of death [1]. PE is the third leading cause of cardiovascular death in the United States, after acute myocardial infarction and stroke. The in-hospital mortality rate is reported to be approximately 12% [2]. Deep vein thrombosis (DVT) plays a particularly important role in its etiology. PE can occur in approximately 30-50% of patients with DVT [3]. Coagulation disorders, heart failure, immobility due to sedentary lifestyle, hyperlipidemia, hypertension, the elderly, patients requiring long-term hospitalization after surgery or bone fractures, obesity, pregnancy, and oral contraceptive use pose a risk for DVT and PE [4]. When PE develops, many complications may occur, including an increase in right ventricular load and an increase in pulse rate, resulting in increased pulmonary vascular resistance and death [5]. Zinc is a trace element with anti-inflammatory effects, found in the structure of more than 300 metalloenzymes, playing a role in many vital systems of the body such as growth-development, immune system, apoptosis and antioxidant system through DNA-RNA replication [6]. Zinc has been shown to contribute to vascular endothelial integrity and to play a role in the release of nitric oxide, a vasodilator [7]. Copper is a trace element found in the structure of many enzymes, such as lysyl oxidase, superoxide dismutase, and tyrosinase, that play a role in redox reactions. Its deficiency and excess can lead to oxidative damage [8]. One study showed that increased copper levels increased C-reactive protein (CRP) levels and increased inflammation [9]. In another study, it was shown that CRP causes thrombus formation by activating platelets and allowing them to adhere to the endothelial surface [10]. Magnesium is the fourth most abundant element in the body, crucial for vital functions [11]. Magnesium is involved in energy production pathways and is part of the ATP complex, essential for muscle contraction, nerve impulse transmission, and normal heart rhythm [12]. It is also necessary for the synthesis of glutathione, which is a part of the antioxidant system, and the glutathione peroxidase

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enzyme, which breaks down hydrogen peroxide, one of the oxidant molecules [13]. Magnesium deficiency causes many diseases such as hypertension, atherosclerosis, Alzheimer's disease, type 2 diabetes and asthma [14]. Iron is an element that plays a critical role in human life, is found in the structure of proteins and enzymes, takes part in ATP production through oxidative phosphorylation, and is important in many syntheses such as DNA synthesis [15]. However, it has been found that in excess, it increases oxidative stress by causing the formation of hydroxyl ion, one of the strongest free radicals known, especially through the Fenton reaction [16]. This study aimed to investigate changes in the levels of vital trace elements zinc, copper, magnesium, and iron in patients with pulmonary embolism. It also aimed to investigate the association of these parameters in the etiology of the disease and their potential role as associated markers for the condition.

Material and Methods

This study was conducted with the decision of Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethics Committee dated 08.09.2025 and numbered 2025/22. As this was a retrospective study, the requirement for written informed consent was waived by the committee. A retrospective study was conducted on a total of 52 individuals, including 26 non-smoking patients with no known chronic disease and no chronic drug treatment (Group I) who applied to Kahramanmaraş Sütçü İmam University Faculty of Medicine Hospital Chest Diseases Clinic between September 1, 2023 and September 1, 2025, with complaints of cough, hemoptysis, chest pain and dyspnea and were diagnosed with pulmonary embolism confirmed by computed tomography pulmonary angiography and 26 age-matched healthy individuals with no complaints, non-smoking patients, no chronic disease and no chronic drug treatment (Group II).

Patients with malignancy, chronic renal or hepatic failure, autoimmune diseases, acute or chronic infections, hematological disorders, or those receiving anticoagulant, corticosteroid, or trace-element supplementation therapy were excluded from the study.

Analyses

Magnesium and iron levels were analyzed using a Cobas e 702 autoanalyzer (Roche Diagnostics, F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland) and measured using the colorimetric method. Serum zinc and copper levels were measured using a flame atomic absorption spectrophotometer (Perkin Elmer Analyst 800, USA). For copper, calibration standards were prepared from a 1000 mg/L stock standard solution (Sigma Aldrich) at concentrations of 50, 100, 150, and 200 µg/dL. For zinc, calibration standards were similarly prepared at 50, 100, 150, and 200 µg/dL from a 1000 mg/L stock standard (Sigma Aldrich). Samples and standards were diluted 1:2 with glycerol (10% for copper, 5% for zinc) prior to measurement. A hollow cathode lamp specific for each element was used, and absorbance was measured at 324.8 nm for copper and 213.9 nm for zinc with an air–acetylene flame. Unknown concentrations were calculated based on the calibration curves. Certified reference materials (Sigma Aldrich, TraceCERT®) and internal quality controls were used to validate the accuracy and precision of the measurements.

Statistical Analysis

All statistical analyses were performed using the Statistical Package (SPSS, version 27.0; IBM Corp., Armonk, NY, USA). Graphs were created with GraphPad Prism (version 10.4.1; GraphPad Software, San Diego, CA, USA). Data distribution was assessed both visually (through histograms and probability plots) and analytically (Shapiro-Wilk test). Normally distributed variables are presented as mean ± standard deviation (SD), non-normally distributed variables as median [interquartile range, IQR], and categorical variables as frequency and percentage (n, %). Between-group comparisons of sociodemographic, clinical, and outcome variables were performed using the Pearson chi-square test, independent samples t-test, or Mann-Whitney U test, as appropriate. To identify risk factors for embolism development, multivariate logistic regression analysis was performed, adjusted for age and sex, and this analysis included serum trace elements that showed significant between-group differences. Model assumptions were verified before analysis, and multicollinearity was assessed using the variance inflation factor (VIF) and tolerance values (VIF < 10, tolerance > 0.1), and adequate sample size was confirmed according to the per-event variable criterion (EPV ≥ 10). A p-value < 0.05 was considered statistically significant. Although the sample size (n = 52) met the minimum criteria for the exploratory multivariate model, the study's statistical power is limited, and the results should be interpreted as hypothesis-generating rather than definitive.

Results

No significant differences were observed between the groups in terms of age and gender distribution (p = 0.781 for both). However, significant differences were observed in serum trace element levels. Zinc and magnesium levels were significantly lower in the embolism group compared to healthy participants (p = 0.003 and p = 0.004, respectively), while copper levels were significantly higher in the embolism group (p < 0.001). Serum iron levels were also significantly lower in the embolism group (p < 0.001) (Table 1).

Multivariate logistic regression analysis, adjusting for age and gender, revealed that higher serum copper levels were significantly associated with an increased risk of embolism (OR = 1.045, 95% CI = 1.012-1.080, p = 0.007). Magnesium levels showed a borderline protective effect, with lower values tending to increase the risk of embolism (OR = 0.013, 95% CI = 0.000–1.009, p = 0.050). Consequently, copper emerged as the strongest associate, while magnesium showed a potential protective role (Table 2).

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Table 1. Comparison of demographic and serum micronutrient concentrations between groups

Variable	All participants (N = 52)	Healthy group (N = 26)	Embolism group (N = 26)	p-value
Age, (years)[a]	65.5 ± 11.8	66.0 ± 11.7	65.1 ± 12.1	0.781
Gender, (F), n (%)	27 (52.9)	13 (50.0)	14 (53.8)	0.781
Zinc, (µg/dL)[b]	66.45 (41.97)	94.70 (42.33)	60.30 (24.87)	0.003
Copper, (µg/dL)[a]	109.07 (37.88)	80.95 (21.95)	126.45 (46.03)	< 0.001
Magnesium, (mg/dL)[b]	1.90 (0.40)	2.05 (0.40)	1.75 (0.52)	0.004
Iron, (µg/dL)b	51.45 (49.85)	67.85 (84.88)	36.30 (38.53)	< 0.001

a: mean ± standard deviation, b: median (Interquartile range)

Table 2. Multivariate logistic regression analysis adjusted for age and sex to identify risk factors for embolism

Variable	Odds ratio (OR)	95% CI for OD	p-value
Zinc	0.982	0.948 to 1.018	0.333
Copper	1.045	1.012 to 1.080	0.007
Magnesium	0.013	0.000 to 1.009	0.050
Iron	0.964	0.924 to 1.006	0.088

Discussion

The most significant finding of our study is that serum trace element levels undergo substantial alterations in patients with PE compared to healthy individuals. Specifically, we demonstrated that copper levels are significantly elevated, while zinc, magnesium, and iron levels are notably decreased in the acute phase of PE. Furthermore, our multivariate logistic regression analysis highlighted that high serum copper levels are independently associated with an increased risk of embolism. These results suggest that the biochemical imbalance of trace elements may be linked to the vascular endothelial stability and oxidative stress mechanisms involved in the clinical presentation of PE. PE continues to be a significant cause of morbidity and mortality in clinical practice due to diagnostic challenges and high mortality rates of up to 30%. In PE, pulmonary circulation is blocked, the right ventricle dilates due to increased workload, wall tension increases, cardiac output and coronary perfusion decrease, and if it persists, heart failure, hypoxemia, and tachycardia occur [17]. Computed tomography and pulmonary angiography are frequently used in the diagnosis of PE. Its etiology includes diseases such as DVT and thromboembolism, coagulation disorders, immobility, various lipidemias, hypertension, pregnancy, cancer, the postoperative period, diabetes, and increased oxidative stress [4,8]. Zinc is a trace element found in the structure of many enzymes, plays a role in the stabilization of cell membranes and vascular endothelium, has anti-inflammatory effects, is important in the development of the immune system, and is involved in DNA and RNA synthesis [6]. One study has shown that zinc lowers blood pressure, increases blood flow, and causes vasorelaxation [18,19]. Levels of CRP, an acute-phase reactant induced by interleukin (IL)-6 and tumor necrosis factor (TNF) and increased during inflammation and infection, were found to be increased by copper and decreased by zinc [9,20]. In our study, zinc levels were found to be significantly lower in PE patients compared to the control group. We believe that low zinc levels impair vascular endothelial stability, reduce nitric oxide release, and thus increase the risk of thromboembolism secondary to vasoconstriction. Furthermore, we believe that the oxidant system may be dominant in zinc deficiency, which would increase the risk of thromboembolism. Copper is a trace element found in the structures of many enzymes, such as lysyl oxidase, superoxide dismutase, and tyrosinase. In excess, it causes oxidative damage via the Fenton reaction due to hydroxyl ions and increases CRP, a parameter of inflammation [8]. Copper levels have been shown to be increased in PE [21,22]. In our study, copper levels in PE were found to be significantly higher than in the control group. Furthermore, in this study, multivariate logistic regression analysis showed that high serum copper levels were significantly associated with an increased risk of embolism. We believe that increased copper levels increase the formation of hydroxyl ions and subsequently damage the vascular endothelium, thus predisposing to embolism. Magnesium is a trace element essential for ATP utilization, nerve conduction, cardiovascular contraction and rhythm maintenance, and the antioxidant system [12]. Magnesium administration in PE patients has been shown to reduce pulmonary vascular resistance and regulate cardiac circulation [23]. In our study, magnesium levels were found to be significantly lower in PE patients compared to the control group. We believe that decreased magnesium levels lead to inadequate ATP utilization, which in turn leads to inadequate nerve conduction and muscle contraction, increasing the risk of vascular thromboembolism. We also believe that magnesium is essential for antioxidant system function, and therefore, its deficiency shifts the balance in favor of the oxidant system,

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damaging the vascular endothelium and leading to PE. Iron is an element found in the structure of many proteins and enzymes, such as hemoglobin, and its deficiency and excess have been shown to cause oxidative damage [15]. A recent study demonstrated a possible association between increased RDW levels and diseases such as deep vein thrombosis and PE [24]. This study found that iron levels were significantly lower in PE patients compared to the control group. We believe that iron deficiency may lead to oxidative damage to the vessels due to the dysfunction of catalase, an iron-containing antioxidant enzyme, and thus to PE We also think that the catalase enzyme, which breaks down hydrogen peroxide, a free radical, contains iron, and in iron deficiency, the catalase enzyme cannot break down hydrogen peroxide, thus causing oxidative damage and thromboembolism [25].

This study has several limitations that should be acknowledged. First, the retrospective and observational design precludes drawing any causal inferences; our findings demonstrate associations rather than direct pathogenesis. Second, the study was conducted with a limited number of participants from a single tertiary healthcare institution. Although we aimed for a larger cohort, the final sample size was restricted by our strict exclusion criteria, which were necessary to eliminate potential confounding factors; nonetheless, this may affect the generalizability of the results.Third, the use of a completely healthy control group may introduce bias, as trace element levels are known to be influenced by general inflammation, acute stress, and severe illness. Future studies should compare PE patients with symptomatic but PE-negative controls or DVT-only patients to isolate PE-specific changes.

Furthermore, due to the retrospective nature of the data, we lacked clinical parameters such as the PESI score, right ventricular dysfunction markers, Troponin, BNP, and thrombus burden. Consequently, we could not evaluate the correlation between trace elements and disease severity or mortality. We also did not perform a head-to-head comparison between these trace elements and established biomarkers like D-dimer. Finally, the small sample size (n = 52) limits the statistical power of our multivariable modeling. Therefore, our results should be interpreted as hypothesis-generating and need to be validated in larger, prospective multicenter cohorts.

Conclusion

It is important to prevent pulmonary embolism as it reduces the quality of life and even causes death. In this study, we found that copper levels increased and zinc, magnesium, and iron levels decreased in patients with pulmonary embolism. We believe these parameters are associated with the disease and may offer valuable insights into the biochemical alterations and clinical status associated with pulmonary embolism. Furthermore, considering the potential link between trace element imbalances and PE, investigating the effects of correcting these deficiencies would be beneficial in future studies.

Ethical Approval

This study was conducted with the decision of Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethics Committee dated 08.09.2025 and numbered 2025/22.

Patient Consent

Due to the retrospective nature of the study, the requirement for written informed consent was waived by the local ethics committee. however, patient data were anonymized and handled in accordance with the Declaration of Helsinki

Conflict of Interest

The authors confirm the absence of any conflicts associated with this work.

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