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Original Article

Association of serum calcium, phosphorus, and vitamin D Levels with clinical severity in patients with chronic obstructive pulmonary disease: A single-center study

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Abstract

Introduction: This study aimed to evaluate serum concentrations of calcium, phosphorus, and vitamin D in patients diagnosed with chronic obstructive pulmonary disease (COPD).

Methods: This study was conducted at the Mashhad University of Medical Sciences, Iran, between 2021 and 2022, focused on assessing the neutrophil-to-lymphocyte ratio (NLR) in COPD patients. Data was collected from clinical files, laboratory results, and direct patient interviews, with an emphasis on demographic data, medical history, and a variety of laboratory and clinical parameters. COPD severity was assessed using clinical criteria and spirometry.

Results: The study included 49 COPD patients, with a mean age of 62.3 ± 8.70 years, 59% of whom were male. Common comorbidities included hypertension (43%) and diabetes (12%). Serum analysis indicated an average calcium level of 9.50 mg/dL and vitamin D3 level of 26 ng/ml. Most patients were prescribed SEROFLO (82%) and TIOVA (92%). Severity of COPD was categorized as 49% in mMRC Grade 2, 43% in AECOPD Category 0, and 67% in GOLD Grade 2. A significant variation in vitamin D3 levels was observed across different GOLD Spirometry Classifications ($P = 0.02$). However, there was no significant correlation observed between calcium and phosphorus levels and COPD severity indicators.

Conclusion: The study revealed a significant variation in vitamin D3 levels among different GOLD Spirometry Classifications in COPD patients, suggesting that vitamin D3 may play a role in the severity of COPD. However no significant association was found for calcium and phosphorus levels with COPD severity, their role should not be disregarded and warrants further investigation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a notable pulmonary disorder characterized by persistent respiratory challenges and diminished airflow, frequently causing inflammation in the pulmonary system. COPD incidence is particularly elevated in low- to medium-income countries where populations face higher exposure to contributing risk factors. The constrained availability of cost-effective healthcare and diagnostic resources in these regions, underscores the imperative for crafting reliable and cost-efficient markers to track the evolution and severity of COPD.[1]

Understanding the pathophysiology of COPD involves recognizing the complex interplay of chronic inflammation and structural changes leading to the limitation of airflow. While systemic inflammation markers, like C-reactive protein (CRP), have been associated with the severity of COPD, the influence of minerals and bone-related disorders has received less attention.[2,3] Calcium and phosphorus are pivotal for cell functions, and their dysregulation can potentially impact lung function and structure.[4,5] Similarly, vitamin D, aside from its established role in bone metabolism and calcium balance, has garnered interest for its immune-modulating properties, which may have implications for pulmonary diseases.[6,7]

In light of this, in this study we aimed to investigate the serum levels of calcium, phosphorus, and vitamin D3 in patients with COPD and find the possible correlation of these biomarkers with the severity of the disease, offering insights into their potential role in the pathogenesis and progression of COPD.

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Study Highlights

What is current knowledge?

- The association between systemic inflammation markers like C-reactive protein with the severity of COPD is established. However, circulating level of calcium and phosphorus, and vitamin D has received less attention. Calcium and phosphorus are pivotal for cell functions. Their imbalance may impact lung function and structure. Vitamin D has garnered interest for its immune-modulating role, which may impact pulmonary function.

What is new here?

- Vitamin D3 levels showed a significant variation among different GOLD grades in COPD patients. Circulating levels of calcium and phosphorus showed no significant association with COPD severity.

Methods

Study Design and Participants

This cross-sectional study was conducted at the Imam Reza Hospital, affiliated with Mashhad University of Medical Sciences, in Mashhad, Iran, from 2021 to 2022. We aimed to evaluate the serum levels of calcium (Ca), phosphorus (P), and vitamin D in patients diagnosed with COPD.

Participants were selected according to specific inclusion criteria: individuals aged between 40 and 80 years who provided informed consent and had a confirmed diagnosis of COPD, as determined by clinical symptoms, spirometric criteria, and a pulmonologist's assessment. Exclusion criteria included patients with active infections, hematologic malignancies, those on certain treatments like oral corticosteroids, and those experiencing an acute exacerbation of COPD at the time of evaluation. The study encompassed a total of 49 COPD patients, selected based on these criteria.

Data Collection and Assessments

Efficient data retrieval was achieved by meticulously inspecting patients' clinical documentation and laboratory findings, enhanced by face-to-face interviews. Captured demographic variables included age, gender, profession, and certain lifestyle behaviors like smoking and drug use. Detailed clinical chronicles, including comorbidities such as ischemic heart disease (IHD), hypertension (HTN), and diabetes mellitus (DM), were also acquired.

For laboratory evaluations, serum levels of Ca, P, and vitamin D were measured. Clinical metrics, gleaned from both documentation and discussions, were used to ascertain COPD's severity. This included tools like the Acute Flare-Up of Chronic Obstructive Pulmonary Disease (AECOPD) classifications, the adapted Medical Research Council (mMRC) Breathlessness Scale, the Worldwide Strategy for Chronic Obstructive Lung Ailment (GOLD) Spirometry Grading, and GOLD's Combined Assessment scales. The COPD Evaluation Test (CAT) was further employed, based on interview responses, to discern the disease's impact on individual health.

Lung function was rigorously determined via spirometric measures, emphasizing values like the one-second forced expiratory volume (FEV1) and the FEV1 to forced vital capacity (FVC) proportion. These values were also culled from clinical records. The corrected calcium levels were utilized, accounting for serum albumin variations, rather than raw serum calcium measurements. This correction ensures a more accurate assessment of the calcium status, as albumin can significantly influence calcium concentration in the blood. Thus, throughout this report, any reference to 'calcium' pertains to this adjusted value, which provides a more reliable indicator of the physiologically active calcium available in the patient's circulation, offering a nuanced understanding of the mineral's role in the pathophysiology of COPD.

Statistical Analysis

The analysis involved SPSS version 26 (IBM Corp., Armonk, NY, USA) and R software version 4.0.2. Descriptive analytics, included counts, proportions, averages, and standard deviations (SD). The Kolmogorov-Smirnov test ascertained the distribution normalcy of unbroken variables. Owing to the skewed distribution of most continuous variables, non-parametric methodologies were favored. The relation of neutrophil-to-lymphocyte ratio (NLR) with diverse metrics was dissected through Spearman's correlation coefficient (rho). A p-value below 0.05 held statistical significance.

Results

Demographic Characteristics of Patients

The baseline demographic and clinical profile of participants in presented in Table 1. In this cohort of 49 participants diagnosed with COPD, the mean age was 62.3 (±8.70) years. Of these, 59% were males, and 41% were females. When considering their occupation, the majority were housekeepers (63%), followed by the self-employed (25%), and workers (13%). The average body mass index (BMI) was noted to be 25.9 (±1.69) kg/m^2. Regarding lifestyle habits, 62% were cigarette smokers, 37% used hookah, and another 37% were exposed to home bakery environments. Opium use was reported by 61% of participants. Clinically, 22% of the patients had a history of IHD, 43% had HTN, and 12% were diagnosed with DM. Serum electrolytes and vitamin levels revealed an average serum calcium level of 9.50 (IQR: 9.20, 9.60), a serum phosphorus level of 3.70 (IQR: 3.50, 4.00), and serum vitamin D3 level of 26 (IQR: 20, 37). In terms of medication, 82% were on SEROFLO, 92% were prescribed TIOVA, while fewer numbers were on medications such as SPIRIVA, Seretide, Symbicort, FORADIL, Theophylline,

Table 1. Baseline demographic and clinical profile of a cohort of patients: a descriptive analysis

Variable	N = 49[a]
Age (years)	62.3 (8.70)
Gender	
Male	29 (59%)
Female	20 (41%)
Occupation	
Housekeeper	5 (63%)
Self-employed	2 (25%)
Worker	1 (13%)
BMI (kg/m^2)	25.9 (1.69)
Smoking Habits	
Cigarette	29 (62%)
Hookah	18 (37%)
Home Bakery	18 (37%)
Substance Use (Opium)	30 (61%)
IHD	11 (22%)
HTN	21 (43%)
DM	6 (12%)
Serum Ca level (mg/dL)	9.50 (9.20, 9.60)
Serum P level (mg/dL)	3.70 (3.50, 4.00)
Serum vitamin D3 level (ng/mL)	26 (20, 37)
Medication	
SEROFLO®	40 (82%)
TIOVA®	45 (92%)
SPIRIVA®	2 (4.1%)
Seretide®	2 (4.1%)
Symbicort®	1 (2.0%)
FORADIL®	1 (2.0%)
Theophylline	1 (2.0%)
Azithromycin	1 (2.0%)

[a] Median (IQR) or Frequency (%).
IHD (Ischemic heart disease), HTN (Hypertension), DM (Diabetes mellitus), SEROFLO® (salmeterol/fluticasone), TIOVA® (tiotropium bromide), SPIRIVA® (tiotropium bromide), Seretide® (salmeterol/fluticasone), Symbicort® (budesonide/formoterol), FORADIL® (formoterol), Ca (Calcium), P (Phosphate), and Vitamin D3.

and Azithromycin.

Characteristics of COPD Severity in Patients

Table 2 shows COPD severity in patients. Upon assessing COPD severity using the mMRC Dyspnea Scale, we found that 10% were classified as Grade 0, 33% as Grade 1, 49% as Grade 2, and 8.2% as Grade 3. Using the AECOPD categories, 43% were in Category 0, 35% in Category 1, and 22% in Category 2. The GOLD Spirometry Classification showed 67% in Grade 2, 29% in Grade 3, and 4.1% in Grade 4. When assessed by the CAT Grade, 6.1% were in Grade 1, 51% in Grade 2, and 43% in Grade 3. Lastly, using the GOLD Combined Assessment, 4.1% were in Category 1, 63% in Category 2, and 33% in Category 42.

Table 2. COPD severity assessment in patients

Variable	N = 49 Frequency (%)
mMRC	
Grade 0	5 (10%)
Grade 1	16 (33%)
Grade 2	24 (49%)
Grade 3	4 (8.2%)
AECOPD	
Category 0	21 (43%)
Category 1	17 (35%)
Category 2	11 (22%)
GOLD	
Grade 2	33 (67%)
Grade 3	14 (29%)
Grade 4	2 (4.1%)
CAT grade	
Grade 1	3 (6.1%)
Grade 2	25 (51%)
Grade 3	21 (43%)
GOLD combined	
Category 1	2 (4.1%)
Category 2	31 (63%)
Category 4	16 (33%)

mMRC (Modified Medical Research Council Dyspnea Scale), AECOPD (Acute exacerbations of chronic obstructive pulmonary disease), GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages, and CAT (COPD Assessment Test) grades.

Comparative Analysis of Calcium, Phosphorus, and Vitamin D3 Across Various COPD Clinical Assessment Scales

The independent-samples Kruskal-Wallis test was used to compare serum calcium, phosphorus, and vitamin D3 levels across different COPD clinical assessment scales (Table 3). Notably, in the context of the mMRC scale, the vitamin D3 level showed a trend towards significance ($P = 0.07$). Meanwhile, the GOLD Spirometry Classification revealed a significant difference in vitamin D3 levels among different grades, with $P = 0.023$.

Discussion

This study aimed to assess serum concentrations of calcium, phosphorus, and vitamin D in patients diagnosed with COPD and to explore the associations of these metabolic elements with the disease's severity. Our findings reveal a significant variance in vitamin D3 levels across GOLD Spirometry Classifications.

Consistent with the findings of Menon et al,[8] our results indicate that lower vitamin D levels correlate with greater disease severity. Similarly, Jorde et al[9] reported a fair correlation between serum 25-hydroxyvitamin D and current FEV1, and we noted an analogous trend, though our study expands upon this by including comprehensive

Table 3. Serum Ca, P, and vitamin D3 levels in relation to COPD severity scales

Variable	Ca Mean (SD)	P Mean (SD)	Vitamin D3 Mean (SD)
mMRC	$P^1 = 0.51$	$P^1 = 0.82$	$P^1 = 0.07$
Grade 0	9.600 (0.223)	3.900 (0.514)	17.80 (4.604)
Grade 1	9.437 (0.508)	3.668 (0.532)	31.14 (13.70)
Grade 2	9.429 (0.399)	3.754 (0.434)	32.53 (17.59)
Grade 3	9.775 (1.826)	3.875 (0.411)	37.00 (11.34)
AECOPD	$P^1 = 0.96$	$P^1 = 0.46$	$P^1 = 0.47$
Category 0	9.385 (0.397)	3.685 (0.531)	29.30 (16.83)
Category 1	9.476 (0.454)	3.782 (0.444)	33.38 (16.88)
Category 2	9.654 (1.061)	3.827 (0.382)	30.38 (10.35)
GOLD	$P^1 = 0.70$	$P^1 = 0.16$	$P^1 = 0.02$
Grade 2	9.439 (0.491)	3.806 (0.419)	28.47 (12.06)
Grade 3	9.557 (0.893)	3.707 (0.535)	39.23 (18.98)
Grade 4	9.550 (0.070)	3.150 (0.494)	11.50 (7.778)
CAT grade	$P^1 = 0.73$	$P^1 = 0.61$	$P^1 = 0.15$
Grade 1	9.500 (0.000)	4.066 (0.602)	19.66 (2.081)
Grade 2	9.456 (0.425)	3.744 (0.433)	29.15 (13.56)
Grade 3	9.500 (0.833)	3.714 (0.494)	34.51 (17.61)
GOLD combined	$P^1 = 0.95$	$P^1 = 0.13$	$P^1 = 0.23$
Category 1	9.500 (0.000)	4.350 (0.494)	18.50 (0.707)
Category 2	9.435 (0.507)	3.771 (0.397)	29.14 (12.17)
Category 4	9.556 (0.831)	3.637 (0.548)	35.76 (20.15)

[1] Independent-Samples Kruskal-Wallis Test.
mMRC: Modified Medical Research Council, COPD: Chronic obstructive pulmonary disease, AECOPD: Acute exacerbations of chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

demographic and clinical profiles. However, unlike Burkes et al,[10] who did not find a direct association between exacerbations and 25-hydroxyvitamin D levels, our study suggests that vitamin D3 may indeed play a role in the exacerbation profile of COPD patients.

The disparity in findings between these studies and ours might be attributable to differences in population demographics, the criteria for COPD exacerbation, or even the methodologies used for measuring vitamin D levels. For instance, the geographical variance and sunlight exposure, as implied by Janssens et al,[11] could contribute to differing baseline vitamin D statuses among study populations. Moreover, while Janssens et al[11] and Menon et al[8] employed the BODE index and CCQ for assessing COPD severity, our study relied on GOLD classifications, which could have influenced the relationship between vitamin D levels and disease markers.

In this study, serum phosphorus levels were measured using a colorimetric method, which is widely used due to its accuracy and cost-effectiveness. Phosphorus levels are quantified based on their ability to react with molybdate, producing a color that can be measured spectrophotometrically. This method allowed for consistent and reliable readings of serum phosphorus levels in the COPD cohort. While our results did not demonstrate a significant association between serum phosphorus levels and COPD severity, the colorimetric measurement approach provided accurate baseline data, underscoring the need for further studies to explore phosphorus's potential role in COPD, particularly in larger cohorts or using longitudinal designs.

Regarding the association between serum calcium levels and COPD stages, Karthik et at[12] observed a significant relationship between decreased serum calcium levels and advanced stages of COPD. In Karthik and colleagues' study, severe hypocalcemia was more prevalent in later stages (III + IV) than in the early stages (I + II), which suggests that as the severity of COPD increases, calcium metabolism might be increasingly impaired. This correlation is essential as it adds another layer to our understanding of COPD as not only a pulmonary condition but also one with systemic manifestations, including significant alterations in nutritional and metabolic status. In contrast, the Wan et al study's results, sourced from the UK Biobank, presented a different aspect of the calcium-COPD relationship.[13] Wan and colleagues' research indicates a positive association between higher serum calcium concentrations and increased risk of COPD incidence and mortality, suggesting hypercalcemia as a risk factor for COPD development and progression. This seemingly contradictory observation could be reconciled by considering that while hypocalcemia is related to advanced disease stages and may reflect a state of disease exacerbation or chronicity, hypercalcemia may be an independent risk factor for the onset and poor outcomes in COPD. The hypercalcemia observed could be related to other pathophysiological processes, possibly linked to comorbid conditions such as primary hyperparathyroidism or malignancies which are known to be associated with increased serum calcium. Meanwhile, in our study there were not any significant difference across calcium levels in COPD severity.

It is important to note the potential influence of albumin-corrected calcium concentrations in the interpretation of the Wan study, as the adjustments for albumin may reveal more about the bioactive calcium status. The large cohort and extended follow-up period provide a robust dataset for establishing serum calcium as a possible biomarker for COPD risk assessment and prognosis.

The importance of the mineral metabolism in COPD is further emphasized by Xing and Wang's study, which investigated the levels of serum 1,25-(OH)2VitD3, calcium, and phosphorus.[14] Xing and Wang's results indicate that both calcium and 1,25-(OH)2VitD3 were significantly lower in COPD patients during both acute and stable stages compared to controls, while phosphorus levels were specifically lower in the acute stage. This decline in serum phosphorus levels during acute exacerbations suggests that phosphorus, much like calcium, could play a role in the acute-phase response or be a marker of disease

severity in COPD.

A major strength of our study lies in the simultaneous analysis of calcium, phosphorus, and vitamin D, which offers a more detailed metabolic perspective. However, the cross-sectional nature of our study limits the ability to infer causality.

Conclusion

In this study of COPD patients, we observed the variance in vitamin D3 levels across GOLD Spirometry Classifications suggests a potential role of vitamin D3 in COPD severity. Further studies are warranted to elucidate the implications of these findings and to design targeted interventions for improved patient outcomes.

Authors' Contribution

Conceptualization: Shima Nabavi, Mahnaz Mozdourian, Muhammad Islampanah, Adele Azarshab, Younes Ghanbari
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Software:
Supervision: Shima Nabavi, Mahnaz Mozdourian
Validation:
Visualization:
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Competing Interests

There is no conflict of interest to be declared.

Data Availability Statement

Data will be available upon reasonable request from the corresponding author.

Ethical Approval

This study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2008). The research protocol was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences under the ethical approval code: IR.MUMS.MEDICAL.REC.1401.573.

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Patient Consent Statement

All patients provided their written, informed consent for their anonymized information to be published in this article. They understood that their names and initials will not be published, and due efforts will be made to conceal their identity.

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