



COMPARATIVE ANALYSIS OF BONE METABOLISM PARAMETERS IN LUNG CANCER PATIENTS

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Abstract:

Background: Lung cancer is one of the growing health concerns worldwide due to its high prevalence. Diagnosis of the disease at an early stage may decrease the mortality associated and improve its prognosis. Vitamin D has been reported to have antioncogenic properties and estimation of its levels along with other parameters of bone metabolism may improve the diagnosis of lung cancer.

Methods: Serum levels of vitamin D, calcium, phosphorus and alkaline phosphatase (ALP) in patients with lung cancer before and after standard chemoradiation were estimated in 25 patients with lung cancer before and 4 weeks after standard treatment by chemoradiation. The levels were also analyzed in 25 apparently healthy controls and data was compared among different groups using appropriate statistical analysis.

Results: The levels of vitamin D in lung cancer patients were found to be statistically significantly altered as compared to controls and also after completion of treatment ($p < 0.05$). The levels of ALP were also found to be statistically significantly decreased in patients as compared to controls ($p < 0.05$) but the difference was not statistically significant in patients before and after treatment ($p > 0.05$). Similarly, difference in serum calcium and phosphorus levels in different groups was also not statistically significant ($p > 0.05$).

Conclusions: Estimation of serum vitamin D along with calcium, phosphorus and ALP may aid in improving the diagnosis and understanding the etiopathogenesis of lung cancer.

Keywords: Lung cancer, Vitamin D, Calcium, Phosphorus, ALP, Bone parameters

Introduction:

Lung carcinoma is the most common cancer among men worldwide. The comparatively lower incidence in women may be attributed to lifestyle differences, particularly smoking habits. Due to delayed diagnosis, the majority of patients present with locally advanced stages of the disease at the time of detection [1]. This underscores the urgent need to identify novel biomarkers involved in the pathogenesis of lung cancer, which may facilitate early diagnosis and improve clinical outcomes.

Hypercalcemia is frequently observed in patients with lung cancer and may result from bone metastases or osteoclastic bone resorption. It is generally associated with a poor prognosis. The underlying mechanism involves various humoral factors secreted by tumor cells that disrupt normal calcium regulation. One such factor is parathyroid hormone-related protein (PTHrP), which is produced by several types of tumors [2,3].

Vitamin D, a key hormone in calcium homeostasis, has traditionally been studied for its role in bone health. However, growing evidence suggests its involvement in cancer pathophysiology. Beyond its skeletal actions, vitamin D exhibits anti-carcinogenic and immunomodulatory effects, mediated through the vitamin D receptor (VDR), which regulates several anti-tumorigenic signaling pathways [4]. In lung carcinoma, vitamin D has been shown to exert anti-proliferative effects by arresting the cell cycle at the G1/S checkpoint and inhibiting DNA synthesis and cellular proliferation [4,5].

In addition to calcium, serum phosphorus levels have also been implicated as potential indicators of disease stage and prognosis in lung cancer [6]. Alkaline phosphatase (ALP), an enzyme involved in phosphotransfer reactions, is elevated in conditions involving bone and liver pathology, including metastasis from malignancies such as lung, prostate, and breast cancer. Recently, ALP has emerged as an independent prognostic marker in various cancers, including lung cancer [7,8].

Given these considerations, the present study was designed to evaluate changes in bone metabolism parameters—including vitamin D, calcium, phosphorus, and ALP—in patients with lung cancer, both before and after standard chemoradiation therapy.

Materials and Methods:

The study included 25 newly diagnosed, histopathologically confirmed patients with lung carcinoma and 25 age- and sex-matched healthy individuals as controls. Diagnosis was established through detailed medical history, clinical examination, radiological imaging, and histopathological evaluation. Disease staging was performed according to the American Joint Committee on Cancer (AJCC) 2014 criteria [9].

Patients with stage I and II lung carcinoma received radical external beam radiotherapy (60 Gy in 30 fractions over 6 weeks), along with concomitant cisplatin (100 mg/m², administered every 3 weeks for a total of 3 cycles). Those with stage III and IV disease were treated with palliative external beam radiotherapy (20 Gy in 5 fractions over 1 week).

Participants were categorized into three groups as follows:

- **Group I:** Healthy controls (n = 25)
- **Group IIa:** Histopathologically confirmed lung carcinoma patients prior to treatment (n = 25)
- **Group IIb:** Lung carcinoma patients 4 weeks post-treatment completion (n = 25)

Patients were excluded if they were medically fit for radical surgery, had a history of any chronic illness (other than cancer), or were on concurrent drug supplements or therapies that could affect bone metabolism.

Serum samples were collected from all participants and analyzed for 25-hydroxy vitamin D [25(OH)D] levels using the radioimmunoassay (RIA) method. The assay was performed on a fully automated RIA Analyzer SR300 (Stratec Biomedical AG, Germany) using the Beckman Coulter 25OH Vitamin D Total RIA kit [10]. Serum calcium, phosphorus, and alkaline phosphatase (ALP) levels were measured using an automated biochemistry analyzer (Rx Suzuka, Randox Laboratories, United Kingdom) with standardized assay kits.

Data analysis was conducted using the Chi-square test, Fisher's exact test, paired Student's t-test, and one-way ANOVA (F-test). Correlations between variables were assessed using Pearson's correlation coefficient. A p-value of <0.05 was considered statistically significant.

Results:

The mean age of participants in Group I (healthy controls) was 47 ± 9.14 years (range: 33–70 years), while in Group II (lung carcinoma patients), it was 60.1 ± 11.1 years (range: 39–85 years). Among the 25 lung cancer patients, 21 (84%) were male and 4 (16%) were female; among the controls, 20 (80%) were male and 5 (20%) were female.

In terms of smoking status, 84% (n = 21) of lung cancer patients were smokers, compared to 64% (n = 16) of the control group. The remaining 16% (n = 4) of patients and 36% (n = 9) of controls were non-smokers.

The most common presenting symptoms in lung cancer patients were cough with expectoration and hemoptysis (68%, n = 17), followed by cough with expectoration alone (24%, n = 6), and cough with expectoration and chest pain (8%, n = 2).

Histologically, all patients had squamous cell carcinoma. The majority of cases (68%, n = 17) presented in stage III, while 32% (n = 8) were in stage IV. No patients were diagnosed in stages I or II. Among the stage IV patients, two had evidence of bone metastases.

Biochemical analysis revealed that serum vitamin D levels were significantly reduced in lung cancer patients compared to controls and showed statistically significant improvement following treatment ($p < 0.05$). Serum alkaline phosphatase (ALP) levels were also significantly lower in patients than in controls ($p < 0.05$); however, the difference in ALP levels before and after treatment was not statistically significant ($p > 0.05$). Similarly, changes in serum calcium and phosphorus levels among the three groups were not statistically significant ($p > 0.05$).

The detailed biochemical parameter levels and their comparisons across groups are presented in **Table 1**.

Discussion:

The findings of the present study highlight the significance of evaluating biochemical bone parameters, particularly vitamin D, in patients with lung cancer. Vitamin D is a key regulator of calcium homeostasis, and its serum levels were found to be significantly decreased in lung cancer patients compared to healthy controls ($p = 0.002$). Post-treatment, a statistically significant increase in vitamin D levels was observed ($p < 0.000$). These results are consistent with the findings of Feng et al., who reported an association between lower serum 25-hydroxyvitamin D levels and both an increased risk and poorer outcomes in lung cancer patients. Notably, a 10 nmol/L increase in circulating 25-hydroxyvitamin D was associated with an 8% reduction in lung cancer risk. Furthermore, it has been demonstrated that vitamin D receptor (VDR) expression declines with advancing cancer stages, and certain VDR gene polymorphisms are linked to increased susceptibility to malignancy [11].

Serum calcium and phosphorus levels did not show statistically significant differences among the groups ($p > 0.05$). This aligns with the findings of Seccareccia, who noted that most lung cancer patients present with normal calcium levels, and only about 10–30% exhibit hypercalcemia [2]. In the present study, only two out of twenty-five patients had bony metastases, and their serum calcium levels remained within the normal range. This may be due to the fact that only around 20% of patients with bone metastases develop local osteolytic hypercalcemia, and the individuals in this study may not belong to that subset [2]. Moreover, the mean calcium levels across all study groups remained within the normal range, possibly due to the small sample size and exclusion of individuals with endocrinopathies or other bone disorders.

Similarly, serum phosphorus levels were not significantly different between groups ($p > 0.05$). While levels were slightly low (though still within normal limits), this may be attributed to impaired intestinal phosphate absorption due to vitamin D deficiency. Since most patients in this study had vitamin D deficiency, the resulting mild hypophosphatemia is plausible. Kouloulis et al. previously reported that pre-treatment phosphorus levels in lung cancer patients were often above normal, and serum phosphorus was predictive of disease stage and survival outcomes. However, the current study did not observe a significant change in phosphorus levels before and after treatment, which could again be due to the limited sample size [6].

Regarding alkaline phosphatase (ALP), serum levels were significantly lower in lung cancer patients before treatment compared to healthy controls ($p = 0.04$), but no statistically significant difference was found between pre- and post-treatment levels ($p > 0.05$). The reduced ALP levels in patients may reflect poor nutritional status, a common feature in cancer-related cachexia. Additionally, only two patients had bone metastases, and both had normal ALP levels, which is not unusual, as only a small

proportion of metastatic cases exhibit elevated ALP. ALP remains a molecule of interest in lung cancer research; a study by Miyanaga et al. (1996) identified a heat-sensitive ALP variant in lung cancer patients, with electrophoretic behavior resembling liver ALP and kinetic properties similar to renal ALP. Immunoprecipitation results showed strong reactivity with anti-liver ALP monoclonal antibodies and moderate reactivity with anti-bone ALP antibodies [12]. Elevated serum ALP levels have also been identified as independent prognostic markers in non-small cell lung cancer [13]. In light of these findings, serum vitamin D and ALP, along with calcium and phosphorus, may be considered in the diagnostic and prognostic assessment of lung cancer. These parameters could potentially aid in early detection and guide clinical management. However, further large-scale studies with a focus on patient outcomes are warranted to substantiate these observations.

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Table 1: Comparison of different biochemical parameters in lung cancer patients before (group IIa) and after treatment (group IIb) and healthy controls (group I)

		Group I (n=25)	Group IIa (n=25)	Group IIb (n=25)	p value between n Group I & IIa	p value between n Group I & IIb	p value between n Group IIa & IIb
Vitamin D (ng/dL)	Mean± S.D	29.93±12.07	20.82±6.71	34.04±7.97			
	Range	14.8-76	9-34	17-49	0.002	0.13	0.000
Calcium (mg/dL)	Mean± S.D	9.44±0.58	9.204±0.60	9.16±0.54			
	Range	8.4-10.7	8.2-10.3	7.8-10	0.17	0.08	0.79
Phosphorus (mg/dL)	Mean± S.D	3.5±0.75	3.46±0.67	3.59±0.52			
	Range	1.9-4.5	2.5-4.8	2.8-4.3	0.37	0.5	0.76
ALP (IU/L)	Mean± S.D	74.2±13.8	65.32±15.7	65.88±21.4			
	Range	48-99	39-101	39-119	0.04	0.11	0.9