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Original Article

Correlation Between Vitamin D and Calcium Levels in Patients with Non-Small Cell Lung Cancer Among Sumatera Utara Population

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Abstract

Background: Lung cancer is a multifactorial disease caused by many factors, including genetics and environment. Vitamin D and calcium play a role in cancer. In lung cancer, vitamin D and calcium have been reported to play a role in inhibiting tumor proliferation and metastasis, promoting tumor differentiation and apoptosis, and contributing to immunity. This study aims to determine the correlation between vitamin D and calcium levels in non-small cell lung cancer (NSCLC) patients among North Sumatra population. ***Methods:*** This cross-sectional study involved 52 NSCLC patients from hospitals in North Sumatra, Indonesia between January and April 2023. Serum 25 hydroxyvitamin D and calcium levels were evaluated. Vitamin D levels were measured using manual ELISA kit (Elabscience, USA), while calcium levels were measured using immunoassay method. ***Results:*** The majority of subjects were men (84.6%), with ages ranging from 29 to 70 years with an average age of 55.3 years. Almost all subjects showed deficient levels of vitamin D and normal calcium levels. The frequency of vitamin D levels was 3.8% sufficiency, 17.3% insufficiency, and 78.8% deficiency, while the frequency of calcium levels was 51.9% normal, 5.8% hypercalcemia, and 42.3% hypocalcemia. The average vitamin D level was 15.27 ng/ml and calcium level was 8.72 mg/dl. The Spearman correlation test results showed a very weak positive and not significant correlation between levels of vitamin D and calcium in patients with NSCLC ($r=0.05$, $p>0.05$). ***Conclusions:*** There was no significant correlation between vitamin D and calcium levels in NSCLC patients in the North Sumatra population.

Keywords: ***Lung cancer, Non-small cell lung cancer, Vitamin D levels, Calcium levels, NSCLC.***

Introduction

Lung cancer is the main cause of malignancy in the world, reaching 11.4% of all patients diagnosed with cancer and the lung is one of the causes of death due to cancer [1]. Lung cancer is the leading cause of mortality for both men and women, with lung cancer being the most frequent cancer in males and the fourth most common in women [2]. There are two primary classifications of carcinoma lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [3,4]. Cancer is a multifactoral disease caused by many things including genetics and environment [5].

The most prevalent dietary deficiency in the world is vitamin D deficiency [6]. Apart from its impact on bone, vitamin D is involved in various cellular processes such as cell apoptosis, differentiation, metastasis, angiogenesis, and proliferation [7]. Vitamin D deficiency may be a risk factor for NSCLC, according to case-control studies [8]. Highest levels of 25-hydroxyvitamin D are associated with reduced lung cancer risk and mortality but not with overall survival [9].

Studies show that there is a potential role for calcium in the development of cancer. In addition to its well-known effects on bone health, calcium regulates various cellular processes, including those related to tumorigenesis, such as cell motility, angiogenesis, gene

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transcription, apoptosis, and proliferation. The critical role of calcium in the development of NSCLC remains uncertain [10,11].

This study aimed to determine the correlation between vitamin D levels and calcium levels in non-small cell lung cancer patients among North Sumatra population.

Materials and Methods

This research is a cross-sectional study involving 52 NSCLC patients who met the inclusion and exclusion criteria from hospitals in North Sumatra, Indonesia from January to April 2023. The inclusion criteria for this study were NSCLC patients and those willing to participate in the research stated in writing after receiving an explanation regarding this research (informed consent).

Patients with SCLC and samples that experienced errors or damage during examination, ranging from unrepresentative specimens to staining errors, were exclusion criteria in this study. Serum 25 hydroxyvitamin D and calcium levels were evaluated, where vitamin D levels were measured using a manual ELISA kit (Elabscience, USA), while calcium levels were measured using the immunoassay method. Three categories exist for vitamin D levels: sufficiency (≥30 ng/ml), insufficiency (20-29 ng/ml), and deficiency (0-19 ng/ml). Additionally, calcium levels are divided into three categories: hypocalcemia (<8.4 mg/dl), normal (8.4–10.2 mg/dl), and hypercalcemia (>10.2 mg/dl). The Spearman correlation test was then used to examine the data.

This research has received information about passing ethical review from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara with No. 26/KEPK/USU/2023.

Results

Data on demographic characteristics are displayed in Table 1. The study's patients ranged in age from 29 to 70 years old, with an average age of 55. Most patients who have had treatment are between ages 40 and 60, while most patients who have not received treatment are older than 60. The majority of the patients in this study were men with stage IV, and there was no difference in the number of patients according to the type of cancer cells.

Table 1: Demographic Characteristics

Variable	With Treatment (n=36)	No Treatment (n=16)
Mean age (range), years	53.38 (29-70)	59.68 (38-69)
<40 years, n (%)	3 (8.3%)	1 (6.25%)
40-60 years, n (%)	19 (52.8%)	5 (31.25%)
>60 years, n (%)	14 (38.9%)	10 (62.5%)
Gender		
Male, n (%)	31 (86.1%)	13 (81.2%)
Female, n (%)	5 (13.9%)	3 (18.8%)
Cytology/Histopatology		
Adenocarcinoma	17 (47.2%)	9 (56.2%)
Squamous cell carcinoma	19 (52.8%)	7 (43.8%)
Stages		
III, n (%)	6 (16.7%)	1 (6.25%)
IV, n (%)	30 (83.3%)	15 (93.75%)

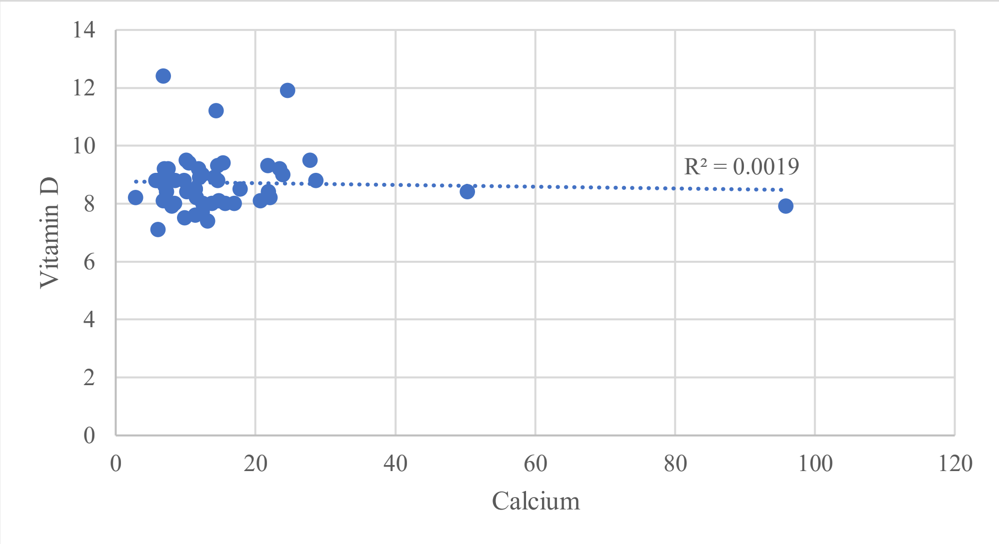
Almost all subjects showed vitamin D deficiency levels. The frequency of vitamin D levels in this study included 3.8% sufficiency, 17.3% insufficiency, and 78.8% deficiency. The frequency of vitamin D levels based on cancer treatment can be seen in Table 2. In patients treated for lung cancer, most patients had deficient vitamin D levels (83.3%), but only 1 patient (2.8%) had sufficient vitamin D levels. A similar thing was also found in patients who had not received treatment, where most patients had deficient vitamin D levels (68.8%), while only 1 patient (6.2%) had sufficient vitamin D levels. The average vitamin D level was 15.27 ng/ml. Based on the treatment, patients receiving treatment had an average vitamin D level of 14.45 ng/ml, compared to 17.10 ng/ml for those not receiving treatment.

In this study, almost all subjects had normal calcium levels. The calcium levels of the individuals were 51.9% normal, 5.8% hypercalcemia, and 42.3% hypocalcemia. Table 2 shows that most cancer patients receiving therapy had normal calcium levels (58.3%). Of the patients receiving treatment, 13 (36.1%) had hypocalcemia and 2 (5.6%) had hypercalcemia. Of the subjects without treatment, the majority of patients had hypocalcemia (56.2%), while 37.5% of patients had normal calcium levels and 6.2% of patients with hypercalcemia. The mean calcium level was 8.72 mg/dl. Based on treatment, the average calcium level was 8.80 mg/dl in patients with treatment and 8.54 mg/dl in patients without treatment (**Table 2**).

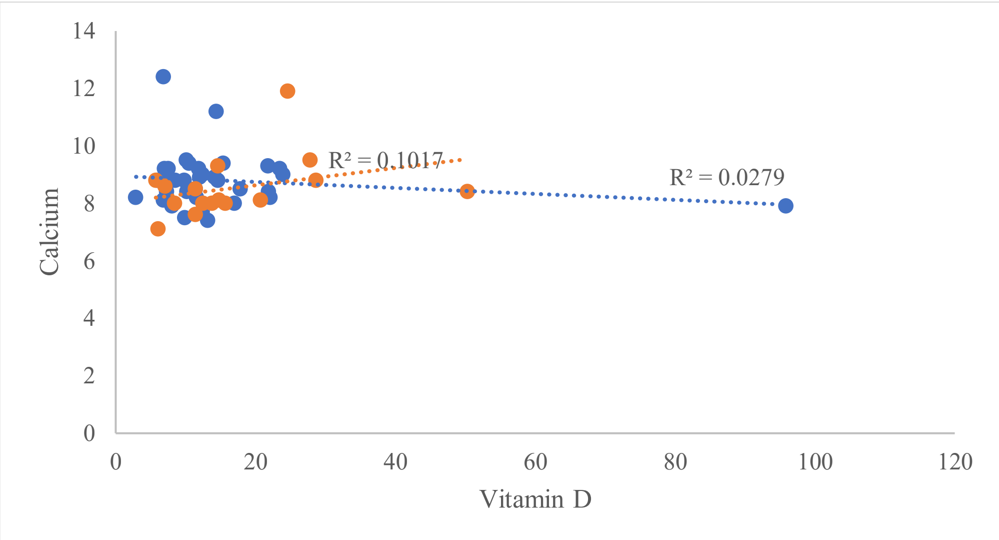
Table 2: Vitamin D and Calcium Levels Based on Cancer Treatment

Variable	With treatment (n=36)	No Treatment (n=16)
Vitamin D		
Mean (range)	14.45 (2.91-95.90)	17.10 (5.74-50.30)
Sufficiency (≥30 ng/ml)	1 (2.8%)	1 (6.2%)
Insufficiency (20-29 ng/ml)	5 (13.9%)	4 (25.0%)
Deficiency (0-19 ng/ml)	30 (83.3%)	11 (68.8%)
Calcium		
Mean (range) mg/dl	8.80 (7.40-12.40)	8.54 (7.10-11.90)
Hypocalcemia (<8.4mg/dl)	13 (36.1%)	9 (56.2%)
Normal (8.4-10.2 mg/dl)	21 (58.3%)	6 (37.5%)
Hypercalcemia (>10.2mg/dl)	2 (5.6%)	1 (6.2%)

The Spearman correlation test results in Graph 1 indicate that there is a very weak positive correlation and statistically non-significant (r=0.05, p>0.05) between calcium levels and vitamin D. The Mann-Whitney test was employed to compare the levels of vitamin D and calcium between patients who had not received treatment and those who were because the data distribution for these two parameters was not normally distributed. According to Graph 2's analytical results, there were no significant differences in either group's vitamin D levels (p>0.05).



Graph 1: Correlation of Vitamin D and Calcium



Graph 2: Correlation between Vitamin D and Calcium in the Treatment and Without Treatment Groups

Discussion

In this study, the majority of lung cancer patients were >40 years old. Lung cancer is relatively rare in individuals younger than 45 years of age. The high-risk group includes patients older than 40 years [2,12]. The majority of patients in this study were male. Epidemiological data shows that the incidence and mortality of lung cancer is higher in men [2,13,14]. The incidence of lung cancer in Indonesia is mostly found in men [1,2].

Cancer is a multifactorial illness that results from a variety of factors, including genetics (5-10%) and environment (remaining factors) [5]. Regarding environmental factors, epidemiological studies show that smoking is the element most strongly related to the occurrence of lung cancer. Furthermore, several lung cancer risk factors need to be considered such as air pollution, infection, environmental carcinogens, and dietary deficiencies [15]. Interactions between nutrition and genetics can influence cancer through modulation of genetic variations, epigenetic modifications in certain populations that permanently change gene expression by interactions or relationships between components and food, as well as cell heterogeneity in certain tumors [5].

Vitamin D is generally obtained from two main pathways in humans, namely synthesis in the skin by exposure to ultraviolet rays from sunlight and direct intake from the diet. Vitamin D is hydroxylated to the circulating form-25-hydroxyvitamin D (25 [OH]D)-in the liver and converted to 1,25-hydroxyvitamin D (1,25(OH)2D3) in the kidneys. Additionally, 25-(OH)D3 has a longer half-life than 1,25(OH)2D3 and is considered an appropriate reflector of serum vitamin D levels [7]. The bioactive form of 1,25-dihydroxyvitamin D [1,25(OH)2D3] acts through the vitamin D receptor (VDR). Studies show that low vitamin D levels are linked to an increased risk of cancer in addition to their impact on bone health [6]. Vitamin D plays a role in the development and progression of various types of cancer and maintaining adequate serum vitamin D levels may be beneficial in the prevention and treatment of cancer [16]. The role of vitamin D against several tumors, including lung cancer, has recently become known [17]. Vitamin D insufficiency is the most prevalent dietary deficiency in the world [6]. Hoffer's research stated that 85% of patients experienced hypovitaminosis D (25-(OH)D levels <75 nmol/L-found in the majority of patients who come to cancer clinics. High intake of vitamin D (or calcium) and serum 25(OH)D levels correlate with a lower risk of lung cancer and a better prognosis [17]. However, the dose-response relationship between lung cancer risk and serum 25-(OH)D levels or dietary vitamin intake is unclear [7,17]. The results of meta-analysis studies show that lung cancer sufferers have deficient vitamin D concentration levels. Lack of physical activity, insufficient sun exposure, and high altitudes can be causes of low vitamin D levels [7].

Numerous processes involving cells, such as apoptosis, differentiation, metastasis, angiogenesis, and proliferation, are influenced by vitamin D. Several mechanisms may explain the protective effect of vitamin D against lung cancer. Several studies show that vitamin D regulates the immunological function of lung epithelial cells and inhibits cellular proliferation and angiogenesis and promotes cell differentiation and apoptosis [18-20]. Vitamin D can increase body immunity by facilitating transcription of the antimicrobial peptide gene cathelicidin and translation of CD14, a co-receptor for detecting bacterial lipopolysaccharide, which are important in innate immunity in the lung [18]. In lung tumor cell lines and mouse models, 1,25(OH)2D3 inhibits angiogenesis and cancer cell growth by suppressing the response to vascular endothelial growth factor (VEGF) [19]. Also, 1,25(OH)2D3 inhibits signaling pathways that promote lung cancer including mutations in K-Ras and epidermal growth factor receptor (EGFR), Wnt/β-catenin dysregulation, which determines metastasis and proliferation [21-23]. Furthermore, 1,25(OH)2D3 regulates the secretion of E-cadherin and catenin, a glycoprotein that aids cell adherence thereby preventing metastasis [24]. Additionally, 1,25(OH)2D3 suppresses the expression of cyclooxygenase-2 and inhibits prostaglandin synthesis, which can stimulate cell proliferation and angiogenesis[25].

In this study, most patients came at an advanced stage. Malignant cells reduce the expression of vitamin D receptors or the conversion of 25-(OH)D to 1,25(OH)2D3 to avoid the antiproliferative action of vitamin D. It can be found more often in advanced stages compared to early stages [17,26].

NSCLC is the most common type of lung cancer, around 80% of lung cancer cases, where adenocarcinoma cells are the most common type [3,4,27]. Various histological types of cancer cells can respond differently to vitamin D. Vitamin D suppresses the growth of lung squamous cell carcinoma (SCC) cell lines, but not adenocarcinoma cell lines where vitamin D receptor mRNA levels in SCC cell lines are higher than in adenocarcinoma cell lines [17,28]. In this study there was no difference in the number of subjects based on the type of lung cancer. Further studies may be needed to assess vitamin D levels based on the histological type of cancer cells.

In this study, it was found that the majority of calcium levels in lung cancer patients were normal. Based on cancer treatment, most patients with treatment have normal calcium levels, while most subjects without treatment have hypocalcemia. Hypercalcemia is a complication in 26% of primary lung cancers. Hypercalcemia can be caused by increased osteoclast activity causing bone calcium to become extracellular fluid caused by bone metastases, or caused by tumor-secreted PTHrP. However, in clinical practice, almost 16% of NSCLC patients have hypocalcemia [10]. According to studies, calcium may have a part in the emergence of cancer. Other than its well-known effects on bone health, calcium intake, and calcium homeostasis can influence cell proliferation, differentiation, and apoptosis, parathyroid hormone and parathyroid hormone-related peptide, vitamin D metabolism and signaling, angiogenesis, and immune responses. Calcium signals regulate cell death and proliferation by activating or inhibiting cellular signaling pathways and calcium-regulated proteins [10,11]. Disruption of calcium homeostasis due to long-term calcium deficiency can promote tumor progression and metastasis [11].

Vitamin D and calcium have important nutritional roles in physiology. In this study, no significant correlation was found between vitamin D and calcium levels in lung cancer sufferers. Recent studies show that signals from extracellular 1,25(OH)2D3 and calcium-sensing receptor (CaSR) receptors can inhibit tumor proliferation and metastasis, promote tumor differentiation and apoptosis, and play a role in immunity. VDR and CaSR are reciprocally regulated and exert anticancer effects simultaneously. The combination of vitamin D and calcium supplements significantly reduces the incidence of lung cancer [29].

Conclusion

There was no significant correlation between vitamin D and calcium levels in non-small cell lung cancer patients in the North Sumatra population. This is being investigated in this initial study. Additional studies comparing the two groups according to treatment are needed.

Declarations

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

There was no financial assistance for this research.

Authors' Contributions

Dina Octafrida Marpaung and Noni Novisari Soeroso were involved in the study's conception and design, data collection, manuscript preparation, and critical revision. Putri Chairani Eyanoer conducted the data analysis and interpreted the results. Elisna Syahruddin and Dina Keumala Sari conducted a critical review. All authors reviewed and approved the final manuscript.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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