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Can vitamin D level be a marker for predicting risk in pulmonary thromboembolism? Comparative evaluation with pulmonary embolism severity index and CT angiography obstruction index

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Abstract

Background/Aim: Venous thromboembolism is a pathological process that is among the leading causes of hospital mortality, and many studies showed that vitamin D receptors have a role in thrombosis. This study aimed to investigate the effect of 25(OH)D deficiency on pulmonary thromboembolism and evaluate the pulmonary embolism severity index (PESI).

Methods: Eighty-one patients over 18 years of age who underwent CT angiography with a pre-diagnosis of pulmonary embolism were included in this case-control study. Groups 1 and 2 consisted of 45 patients with pulmonary embolism (PE), and 36 patients without pulmonary embolism, respectively. The PE patients were divided into five groups in terms of age, gender, fever, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, history of chronic lung disease and heart failure, mental status, and malignancy to calculate the PESI score. Classes 1 and 2 were classified as low-risk, and Classes 3, 4, and 5 as high-risk. The CT obstruction index (CTOI) was calculated in patients with pulmonary embolism. Vitamin D levels were noted.

Results: No significant difference was observed between the groups in terms of age, gender, and body mass index values ($P>0.05$). 25(OH)D level was significantly lower in the pulmonary embolism group (7.2(3.3) vs. 8.7(7.0), $P=0.028$). The CTOI was significantly higher in the high-risk patient group ($P=0.019$).

Conclusions: The evaluation of 25(OH)D levels may be beneficial in determining the risk of thromboembolism.

Keywords: CT obstruction index, PESI score, Pulmonary embolism, 25(OH)D

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Introduction

Vitamin D is essential for maintaining health [1]. In addition to the calcium-phosphorus metabolism, it also affects the immune system, inflammation, anti-oxidation, and anti-fibrosis [2, 3]. Recent studies revealed that chronic diseases, including cardiovascular diseases, diabetes, cancers, autoimmune, and infectious diseases are associated with vitamin D [4-6]. 25(OH)D deficiency is thought to increase inflammation, insulin resistance, pancreatic beta-cell dysfunction, and renin-angiotensin-aldosterone system dysfunction, leading to atherosclerotic and cardiovascular diseases [7]. Numerous studies showed that 25(OH)D receptors have a role in thrombosis and increased 25(OH)D levels reduce the venous thromboembolism (VTE) risk [8, 9].

VTE is a pathological process that includes pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). The current clinical classification used to predict the prognosis in PTE is PESI [10, 11]. CT angiography (CTA) helps to evaluate the presence of thrombus up to the distal segmental branches, and calculate the CTOI, which reveals the extent of the thrombus and the arterial occlusion's degree [12, 13]. Many studies compared the efficiency of PESI and CTOI in evaluating the prognosis [14, 15].

Our study aims to examine the effect of 25(OH)D deficiency on PTE and evaluate the PESI, which helps to predict prognosis, and CTOI findings with 25(OH)D levels comparatively.

Materials and methods

Our study was designed retrospectively and approved by the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (2020/331). Eighty-one patients over 18 years of age who underwent CTA with a pre-diagnosis of pulmonary embolism and signed the consent form between 01.08.2019-01.02.2020 were included in the study. Our study comprised patients who visited the radiology department between these periods and did not match the exclusion criteria. The G*Power 3.1 tool was used to calculate the number of patients to be included in each group, with a confidence interval of 95% and a power of 80%. To avoid bias, the patients who met the inclusion criteria were consecutively grouped. Patients with autoimmune and inflammatory diseases, hypercalcemia, renal failure, sarcoidosis, malignancy, hypophosphatemic rickets, enzyme deficiency, and receptor defects, and patients with suboptimal CTA were excluded from the study. The patients' demographic data, history of ischemic heart disease, diabetes, and hypertension (HT), and laboratory results were recorded.

The patients underwent a CTA examination with a 64-slice CT device (General Electric Revolution EVO, 64-slices). The scan parameters were as follows: 0.6 mm collimation, 1.5 mm slice thickness, 1.4 mm increment, 100kV, 135 mAs, a pitch of 0.9, and a gantry rotation time of 0.33s. According to the results of CT angiography, 45 patients diagnosed with pulmonary embolism constituted Group 1, and 36 patients without pulmonary embolism constituted group 2. The CTOI was calculated in PE patients with the consensus of two radiologists based on the formula used by Qanadli et al. [13]. Pulmonary trunk diameter and the ratio of right ventricle (RV) diameter to the left ventricle (LV) were noted in 45 patients with embolism and 36 patients without embolism, apart from the calculation of vascular obstruction percentage.

No consensus exists about the optimum serum 25(OH)D level. 25(OH)D deficiency indicates 25(OH)D levels<20ng/ml (50nmol/l) in many studies, and insufficiency indicates levels between 21-29 ng/ml. The optimal 25(OH)D concentration is at least 30ng/ml [16]. These reference values were used in our study, as well.

The patients with pulmonary embolism were divided into five groups based on age, gender, fever, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, history of chronic lung disease and heart failure, mental status, and malignancy to calculate the PESI score. Classes 1 and 2 were classified as low-risk, and Classes 3, 4, and 5 as high-risk [17].

Statistical analysis

The analysis was performed with SPSS 20.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA). The normality of the variables was tested with the Kolmogorov-Smirnov method. Quantitative variables were presented as mean (standard deviation) (SD) and median (interquartile range (IQR)) values, while qualitative variables as numbers and percentages. Differences between independent groups were evaluated by *t*-tests and ANOVA for quantitative data and Mann-Whitney U and Kruskal Wallis tests for non-normal variables. A two-tailed *P*-value of <0.05 indicated significance.

Results

Forty-five patients with PE and 36 patients without PE were included in our study. No significant difference was observed between the groups in terms of age, gender, and body mass index values ($P>0.05$). The patients were evaluated in terms of ischemic heart disease, diabetes, HT, hyperlipidemia, and smoking. The mean 25(OH)D level was 7.2(3.3) ng/ml in the PE group with embolism and 8.7(7) ng/ml in the control group ($P=0.028$). In the PE group, 25(OH)D levels were 10ng/ml or less in all patients (severe deficiency), significantly lower than that in the control group (Table 1).

Table 1: Demographic and clinical data and vitamin D level of pulmonary embolism (+) and (-) patients (n=81)

Demographic/Clinical date	Pulmonary embolism (+) (n=45)	Pulmonary embolism (-) (n=36)	*P*-value
Age, (years)	67.4 (16.3)	66.8 (13.4)	0.185
Gender, male (%)	53.3(24)	75(27)	0.045
Body mass index (Kg/m^2)	28.2 (4.8)	26.4 (4.2)	0.427
Ischemic heart disease, n (%)	10(22.2)	1(2.7)	0.011
Diabetes, n (%)	1(2.2)	0	0.368
Hypertension, n (%)	18(40)	12(33.3)	0.537
Hyperlipidemia, n (%)	5(11.1)	0	0.039
History of smoking, n (%)	15(33)	21(58)	0.024
25-Hydroxy Vitamin D (ng/mL)	7.2(3.3)	8.7(7)	0.028

Data are presented as mean (SD) or n (%). 25-hydroxy vitamin D (ng/mL) level is presented median (IR)

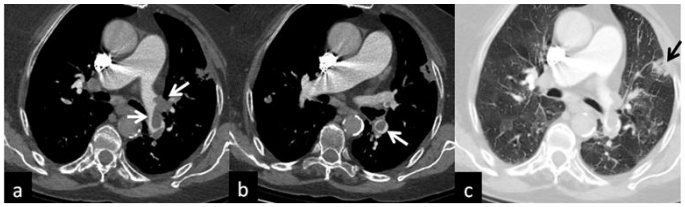
In the PE group, the PESI score was correlated with the CTOI. According to the PESI score, 71% and 29% of the PE patients were in the high and low-risk groups, respectively. The mean CTOI was 36.1 (19.7) in the high-risk group (Figure 1) and 20.8 (17.4) in the low-risk group ($P=0.019$). The mean 25(OH)D levels were 6.84 (2) and 7.19 (1.7) ng/ml in the high and low-risk groups, respectively ($P=0.598$). The data of the PE group are summarized in Table 2.

Table 2: The patient groups with pulmonary embolism (n=45)

	High risk patients (n=32)	Low risk patients (n=13)	*P*-value
CT Obstruction Index	36.1 (19.7)	20.8 (17.4)	0.019
25-Hydroxy Vitamin D (ng/mL)	6.84 (2)	7.19 (1.7)	0.598

Data are presented as mean (SD) or n (%).

Figure 1: 78-year-old patient's CT angiography examination with a massive pulmonary embolism (a, b) (white arrow) and parenchymal infarction (c) (black arrow) In the high-risk group patient, the CT obstruction index was 27 and serum vitamin D level was 3.49 ng/ml.



In both groups, besides the evaluation of CTA in terms of embolism, the diameter of the main pulmonary artery, RV/LV, and superior vena cava (SVC) diameters were also measured. The pulmonary trunk diameters were 29.3 (4.2) mm and 30.1 (3.7) in the PE and control groups, respectively (P=0.049). The ventricular diameter ratio was 1.3 (1.05) in the PE group and 0.95 (0.2) in the control group (P<0.001), and the RV diameter was significantly higher in the PE group.

Discussion

Venous thromboembolism is one of the most critical causes of preventable mortality, especially in the elderly and patients confined to bed, and the relationship between 25(OH)D level and thrombosis was shown in many studies [18]. 25(OH)D level was significantly lower among the PE patients in our study. Besides, our study made a comparative evaluation between 25(OH)D levels and embolism burden as well as the relationship between 25(OH)D and thromboembolism, and it is the first in the literature, as per our research. For this purpose, the PESI score and CTOI, which are related to 25(OH)D levels and embolism burden, were evaluated comparatively. Although mean levels of 25(OH)D were lower in the high-risk group, no significant difference was found. However, 25(OH)D levels were below 10ng/ml (severe deficiency) in all patients with embolism. 25(OH)D deficiency and thromboembolism etiology are multifactorial [1]. Nonetheless, existing studies and ours support that a low 25(OH)D level is associated with thromboembolism. We think that evaluating 25(OH)D levels in patients who constitute the risk group for thromboembolism and who are planned to be hospitalized, and vitamin D addition to the treatment in patients with a deficiency may contribute to reducing the risk of thromboembolism.

Another significant result of our study was the correlation between the PESI score and CTOI in PE patients. The CTOI was significantly higher in the high-risk patient group than in the control group. In contrast to the advancements in prophylaxis, diagnostic methods, and therapeutic options, venous thromboembolism is still a major health problem. Since death usually occurs in the first hours after hospitalization, rapid and specific diagnosis is critical [19]. In addition to detecting the embolism, the ability of CT examination to provide information about the embolic burden and RV load is very valuable for a rapid pre-evaluation. For this reason, the correlation between the PESI score, which contributes to the assessment of the prognosis, but takes time due to the number of parameters, and the CTOI, which provides information about the embolism burden, and the inclusion of the ventricle diameter ratio, can provide a quick and objective assessment of the patient prognosis.

Thromboembolism patients were shown to have low 25(OH)D levels in many studies, as in ours. In a cohort study conducted by Lindqvist et al. [9] on 40,000 women followed for 11 years based on the "Does active sun exposure habit reduce the risk of venous thrombotic events?" question, they found that the risk of venous thromboembolism was 30% lower in Swedish women who sunbathed or used solarium during summer-winter holidays or abroad, compared to those who were not exposed to the sun. Khademvatani et al. [7] investigated the relationship between idiopathic lower extremity DVT and 25(OH)D, and a significantly lower 25(OH)D level was observed in the DVT group compared to the control group.

Although numerous studies [20] and ours support the relationship between 25(OH)D and thromboembolism, studies with larger participants and a longer follow-up are needed.

The correlation between the PESI score and the CTOI, and significantly higher CTOI in the high-risk patient group, were also in line with the literature. In the study of Wu et al. [12], there was a correlation between PE indices, PE volume, and survival, and preliminary evidence showed that clot quantity is a significant predictor of patient death in PE. Qanadli et al. [13] concluded that CTOI and Miller index showed a good correlation. In our study, the calculation method of Qanadli et al. [13] was used as a reference in the calculation of the CTOI. Nural et al. [14] found that CTOI, RV and SVC diameters, RV/LV short-axis ratio, ventricular septum shape, and contrast reflux to the inferior vena cava were useful in distinguishing hemodynamically stable and unstable patients in the patient group with embolism. In our study, the main pulmonary artery diameter, RV/LV, and SVC diameters were measured to predict right ventricular load. Ventricular diameter ratios were 1.3 (1.05) in the embolism group and 0.95 (0.2) in the control group, and the RV diameter was significantly higher in the embolism group.

Limitations

Our study's most significant limitation was the small number of patients. Many studies also showed that 25(OH)D levels were lower in the winter compared to in the summer [9], and that the incidence of thromboembolism increased during the winter [20]. Our study was conducted between August and February, and we could not evaluate the relationship between 25(OH)D, embolism, and seasonal effects. Also, 25(OH)D levels were measured in patients hospitalized due to embolism, but control values were not measured before and after hospitalization. More extensive clinical studies and meta-analyses are needed to demonstrate the effect of vitamin D supplements on thrombosis, since many factors affect 25(OH)D levels, such as genetics, inflammatory causes, and seasonal changes.

Conclusion

25(OH)D levels were significantly lower among patients with thromboembolism in our study, and evaluation and supplementation of 25(OH)D levels in patients at risk for thromboembolism may be beneficial in reducing its risk. Our study suggested that the 25(OH)D level, which is routinely checked in clinical practice, can be used as a marker for pulmonary thromboembolism. Besides, we think that evaluating

the embolism burden as well as the presence of embolism may help objectively predict the prognosis and affect treatment planning in this disease with remarkably high mortality.

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