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The Relationship between Vitamin D Deficiency and Pulmonary Artery Atherosclerosis in Chronic Thromboembolic Patients

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Abstract

Background: Our aim of our study was to determine the relationship between vitamin D level and pulmonary artery's atherosclerosis in patients with chronic pulmonary thromboembolic pulmonary hypertension (CTEPH) who underwent pulmonary endarterectomy (PEA).

Methods: Fifty-six patients with CTEPH who underwent PEA included in our study. Pathologic examination performed to the excised chronic thromboembolic material for the presence of atherosclerosis. We determined patients' 25-OH vitamin D level in our study.

Results: The average 25-OH vitamin D level in the group of the patients with atherosclerosis was lower than the average 25-OH vitamin D level in the patients with no atherosclerosis (9 ± 6.8 and 16 ± 5.9 pg/ml; p=0.005). There were no significant differences between two groups regarding hypercholesterolemia, high sensitive CRP (hsCRP) and the neutrophile-lymphocyte ratio (N/L ratio).

Conclusions: We believe that vitamin D can be routinely used in patients with CTEPH vitamin D. Vitamin D replacement may be protective against atherosclerosis in these patients.

Keywords: Vitamin D; Chronic pulmonary thromboembolism; Pulmonary endarterectomy; Pulmonary atherosclerosis

Introduction

Vitamin D is essential for maintaining calcium and phosphorous homeostasis and in regulating bone formation. In addition to, vitamin D deficiency is associated with increased rates of hypertension [1], peripheral arterial disease [2], myocardial infarction [3,4]. However, vitamin D has found to associate with early signs of atherosclerosis (as increased carotid intima-media wall thickness) [5-7]. We conducted this study to investigate the relationship between vitamin D level and atherosclerosis in chronic thromboembolic patients that examined and atherosclerosis in pulmonary endarterectomy materials.

Methods

The study was the single center and retrospective study. Pathologic specimens of CTEPH patients who underwent PEA between August 2010 and June 2013 examined for the presence of atherosclerosis. Data of 59 patients (patient with atherosclerosis number:24) used for the analysis. Demographic data, cardiovascular risk factors and laboratory findings of all patients recorded. We analyzed pulmonary endarterectomy material regarding pulmonary atherosclerosis. Atherosclerosis was defined intimal thickness and plaque of pulmonary artery as shown in Figures 1 and 2. Sera collected, centrifuged and stored at -70°C until analyzed. Serum 25-OH vitamin D was determined by a direct, competitive chemiluminescence immunoassay (DiaSorin, Stillwater, Minn) [8]. The level of detection for 25-OH vitamin D was <4 ng/ml. This method accurately measures both D2 and D3 together and is reported as a total 25 (OH) vitamin D. The reference range is 32-100 ng/ml. This study identifies vitamin D deficiency according to the Framingham Offspring Study that defines vitamin D deficiency as serum 25 (OH) vitamin D <10 ng/mL. Inclusion criteria were age between 21 and 82 years, chronic thromboembolic patients. Exclusion criteria were

1. any symptoms believed to be related to cardiovascular disease,
2. any evidence of ischemic heart disease,
3. pregnancy.

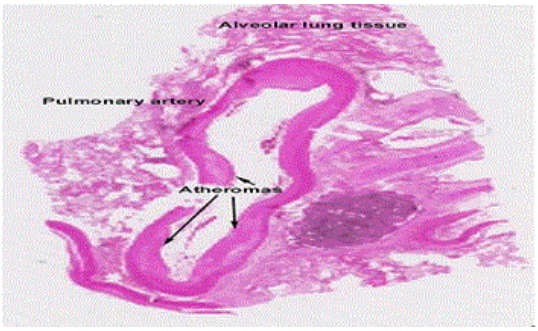

Figure 1: Atherosclerosis image in Pulmonary Artery.

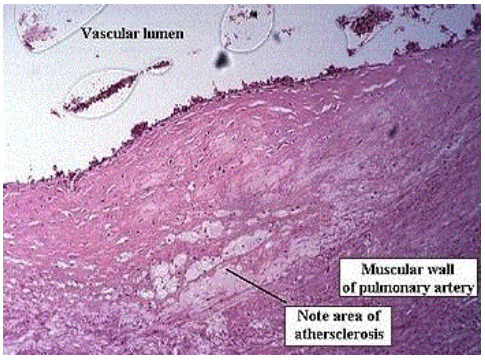

Figure 2: Atherosclerosis image in Pulmonary Artery.

The ethic committee at the Marmara University of Medicine approved the study protocol, and all study participants provided written informed consent. All procedures used in this study were by institutional guidelines.

Statistical methods

Statistical analyses were done using SPSS (Statistical Package for the Social Sciences ver. 13, SPSS Inc., Chicago, Illinois, USA) software. Numeric variables presented as median ± standard deviation; categorical variables presented as percentage values. The equality of the data to the normal distribution assessed with the Shapiro-Wilk test. Since the data did not usually distribute, Mann-Whitney U test, a nonparametric test was used to compare the average values between the groups. Categorical variables were compared using the chi-square test or Fisher's exact chi-square test. p-value <0.05 was set to be significant for our trial.

Results

The study consists of 59 patients with chronic thromboembolic pulmonary hypertension (CTEPH) who underwent pulmonary endarterectomy. We displayed that 24 patients (11 Male, mean age 50.58 ± 15.5) had pulmonary atherosclerosis and 35 patients (18 Male, mean age 50.44 ± 16.88) had without pulmonary atherosclerosis. Clinical characteristics and some cardiovascular risk factors similar between two groups shown in Table 1. However, diabetes, smoking and family history were seen more in without atherosclerosis group shown in Table 2). The average 25-OH vitamin D level was lower in patients with atherosclerosis (9 ± 6.8 and 16 ± 5.9 pg/ml; p=0.005) shown in Table 3. Moreover, according to the ROC curve analysis, the optimal cut-off value of vitamin D to predict atherosclerosis was found as 8 U/ml, with 70% sensitivity and 100% specificity (AUC), 0.817; 95% (CI), 0.630-0.936; P=0.0001) shown in Figure 3.

Parameters	Atherosclerosis Group (A)	Nonatherosclerosis (Group B)	p-value
Age	50.58 ± 15.5	50.44 ± 16.88	0.37
High- Density Lipoprotein	39 ± 13	44 ± 12	0.171
Low-Density Lipoprotein	110 ± 41	111 ± 43	0.828
Triglycerides	111 ± 34	127 ± 64	0.264
Total Cholesterol	172 ± 47	180 ± 49	0.557
High sensitive CRP	30 ± 19	34 ± 21	0.732
Mean Platelet Volume	6.3 ± 1	6.5 ± 1.2	0.4
Neutrophile/Lymphocyte ratio	5.8 ± 3.8	6.6 ± 3.5	0.97

Table 1: Evaluating basic characteristic differences between Group A and Group B.

Parameters	Atherosclerosis (Group A)	Nonatherosclerosis (Group B)
Atherosclerosis	65 (50.8%)	63 (49.2%)
Family history	9 (7%)	119 (93%)
Diabetes	26 (20.3%)	75 (58.6%)
Smoking	18 (14.1%)	83 (64.7%)
Hypertension	13 (20%)	15 (20%)
Gender	Male (46.1%)	Male (53.9%)

Table 2: Characteristic differences between Group A and Group B.

	Number of Patients	Vitamin D average	Standard Deviation	Standard Deviation Mean	P-value
Atherosclerosis	24	16	5.9	1.96	0.005
Nonatherosclerosis	35	9	6.8	1.53	

Table 3: The average 25-OH vitamin D level of two groups.

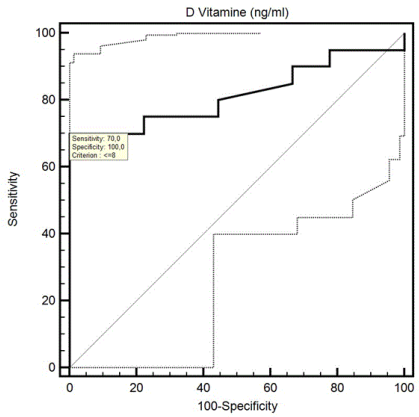

Figure 3: ROC analysis for vitamin d to predict atherosclerosis (area under curve is 0.817).

Discussion

To the best of our knowledge, this is the critical study to demonstrate that vitamin D associated with atherosclerosis in patients with venous thrombosis. We have also shown that vitamin D levels upon admission were related to pulmonary atherosclerosis. Recent studies have found out the functions of vitamin D other than those contained in bone metabolism. Many mechanisms have been asserted to clarify the association between vitamin D and pathophysiology of atherosclerosis since the finding of the entity of vitamin D receptor (VDR) within some cells, e.g., vascular smooth muscle cell and endothelium [8]. It informed that vitamin D deficiency might be a factor in vascular pathology [9]. For example, vitamin D provides tension regulation and prevents cardiac hypertrophy by inhibiting activation of renin [10]. Vitamin D have been demonstrated to inhibit the production of many cytokines (IL-2 and IFN), initiative to a reduction in metalloproteinase and decrease plaque production and instability [11]. Furthermore, it has been demonstrated to have immunosuppressive effects by which it reduces the production of cytokines, which have described as having an important role in atherogenesis [11]. The relationship between vitamin D and atherosclerosis reinforced at a clinical level by Melamed [12]. A similar association of peripheral artery disease and low serum levels of vitamin D were informed by Fahrleitner [13,14]. As far as we know, there is study available in the literature about the association between atherosclerosis and vitamin D deficiency, but our study is first studies that were showing pathological in recurrent thrombosis, it is of importance for this reason. When the two groups compared in our study, vitamin D level of patients with atherosclerotic was significantly lower than vitamin D levels of the nonatherosclerotic group. Our present data show that vitamin D deficiency may be related to atherosclerosis in thrombosis ($p<0.005$). Multiple studies have demonstrated the comparison between vitamin D deficiency-atherosclerosis and venous thromboembolism-atherosclerosis. Moreover, no reports defining the vascular effects of vitamin D deficiency in venous thromboembolic patients. Our study supported that while vitamin D levels correlated with increased atherosclerotic risk as estimated by pulmonary artery's biopsy material, there were no plainly realized functional and structural vascular changes. To our knowledge, studies research the vascular effect of vitamin D status in CTEPH. Vitamin D level may be good a predictor of atherosclerosis in chronic thromboembolic patients. In our trial, the AUC-ROC of 95% reveals that the model is acceptable, with an accuracy (AUC, 0.817; 95% CI, 0.630-0.936; P=0.0001). Another important result is that, contrary to expectations, there was no correlation between the level of CRP and neutrophil/lymphocyte ratio and atherosclerosis. It may be based on the insufficient number of patients. In conclusion, it found in our study that there might be an association between atherosclerosis and vitamin D deficiency. The significant restriction of our study is the limited number of patients. A large-scale research concerning this issue is therefore needed. The authors state that they hold to the Requirements for Ethical Publishing in Biomedical Journals [15].

Conclusion

In summary, patients with CTEPH followed at clinics have the high risk of vitamin D deficiency regarding the risk of atherosclerosis. In consequence, we believe that we must monitör the levels of vitamin D at baseline and during follow-up and supplement vitamin D if any deficiencies detected.

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