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Short Communication

Importance of Vitamin D Deficiency in the Development of Idiopathic Deep Vein Thrombosis

Hasan Ekim[1]* and Meral Ekim[2]

[1]*Department of Cardiovascular Surgery, Bozok University School of Medicine, Turkey*

[2]*Bozok University School of Health, Yozgat, Turkey*

***Corresponding author**

Hasan Ekim, Department of Cardiovascular Surgery, Bozok University School of Medicine, Yozgat, Turkey, Tel: 90535 4176539; Email: drhasanekim@yahoo.com

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Abstract

Background: Currently, venous thromboembolism (VTE) is the common name for both pulmonary embolism (PE) and deep vein thrombosis (DVT). Some studies have reported a relationship between low vitamin D concentrations and VTE. Although the negative effects of vitamin D deficiency on coagulation, fibrinolysis and inflammation have been shown increasingly in both in vitro and animal studies, data from human studies are less conclusive. Therefore, we tried to determine the relationship between DVT and 25-hydroxyvitamin D (25(OH)D).

Methods: A total of 151 participants, including 82 patients with DVT and 69 healthy participants, were included in this study. Serum 25(OH)D and magnesium levels were measured in all participants.

Result: In the patient group, there were 42 men and 40 women with a mean age of 56.73±17.06 years. In the healthy control group, there were 30 men and 39 women with a mean age of 53.28±18.42 years. The mean serum 25(OH)D level of the DVT patients (12.58±6.51 ng/mL) was found significantly lower than the healthy participants (18.75±9.16 ng/mL) ($p<0.03$). Vitamin D deficiency was more frequent in female patients (90%) compared to male counterparts (76.2%), whereas it was about the same frequency in healthy males (50%) and females (48.7%).

Conclusion: Our study supports the view that there may be a relationship between DVT and vitamin D deficiency. Although the number of patients is not sufficient, we can suggest that severe vitamin D deficiency may be a predisposing risk factor to be considered for DVT, especially in FVL carriers. However, our findings should be supported with further studies.

INTRODUCTION

Currently, venous thromboembolism (VTE) is the common name for both pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE has been reported to be the third most common cardiovascular disease associated with mortality [1]. Although many environmental and hereditary predisposing factors are known to be associated with VTE disease, obvious provoking factors were not detected in 30-50% of those patients [2].

Both DVT and vitamin D deficiency are highly prevalent globally [3]. The incidence of vitamin D deficiency even in healthy individuals in Middle East countries was reported to range between 30-50% [4].

Increasing evidence points to a comprehensive interrelationship between inflammation and coagulation, whereby inflammation activity affects not only to activation of coagulation, but coagulation also affects inflammation [5]. The tissue factor, an important initiator for the activation of the extrinsic clotting pathway in vivo, is one of the linkages between coagulation and inflammation [6]. Thus, both hypercoagulability and inflammation have pivotal roles in thrombosis formation [5]. Vitamin D deficiency promotes stimulation of both systemic and vascular inflammation [7]. Indeed, low vitamin D concentrations increase the risk of thrombotic obstruction in saphenous vein grafts [7].

Although the negative effects of vitamin D deficiency on coagulation, fibrinolysis, and inflammation are increasingly demonstrated in both in vitro and animal investigations, data from human investigations are less conclusive [3]. Thus, more human trials are required to reveal the exact relationship between DVT and vitamin D status. We aimed to investigate the relationship between DVT and vitamin D deficiency.

MATERIAL AND METHODS

Our study was performed in Bozok University, Turkey between October 2015 and March 2020. Informed consent was obtained from each participant, and the study was accepted by the Bozok University Ethics Committee (196/07.10.2013).

A total of 151 participants, including 82 DVT patients and 69 healthy individuals, were included. The study was performed during the cold autumn and winter months when exposure to sunlight was lowest. In the patient group, the diagnosis of DVT

was established by physical examination, D-dimer test and venous Doppler ultrasonographic examination. The participants in the control group had no findings suggesting DVT and were healthy in appearance. Fasting blood samples were taken from each participant to measure 25-hydroxyvitamin D (25(OH)D) levels and laboratory testing. Participants with cardiovascular risk factors, renal insufficiency and vitamin D supplementation were excluded.

Since 25(OH)D measurements show both endogenous vitamin D production and exogenous vitamin D intake, the best laboratory parameter of vitamin D concetration is 25(OH)D [8]. Thus, serum 25(OH)D levels were measured to determine vitamin D levels. The 25(OH)D level was classified as deficient (less than 20 ng/mL), insufficient (between 20-29 ng/mL), and normal (more than 29 ng/mL) [1]. 25(OH)D level of less than 10 ng/mL was considered as serious vitamin D deficiency.

In patients diagnosed with DVT, anticoagulant therapy using oral coumadin (warfarin) and parenteral bemiparin (low molecular weight heparin) was initiated, and was continued until targeted INR values were obtained for at least two measurements. Subsequently, oral warfarin treatment alone was continued for at least six months.

STATISTICS

The results were presented as mean± standard deviation. Independent t test was used for statistical analysis. P values of less than 0.05 were accepted as statistically significant.

RESULTS

In the patient group, there were 42 female and 40 males ranging in age from 18 to 89 years with a mean age of 56.73±17.06 years. In the control group, there were 30 men and 39 women ranging in age from 20 to 86 years with a mean age of 53.28±18.42 years. There was no significant difference between the two groups with respect to age (p> 0.4).

25(OH)D levels ranged from 3.0 to 31.5 ng/mL in DVT group and between 3.1 and 48.9 ng/mL in healthy group. The mean serum 25(OH)D level of the DVT patients (12.58±6.51 ng/mL) was found significantly lower than the healthy participants (18.75±9.16 ng/mL) (p<0.03). Vitamin D deficiency was detected in 68 (82.9%) of DVT patients and 34 (49.3%) of healthy subjects (Table 1). Vitamin D deficiency was more frequent in female patients (90%) compared to male counterparts (76.2%), whereas it was about the same frequency in healthy males (50%) and females (48.7%). Severe vitamin D deficiency was detected in 25 (62.5%) female patients and 9 (19.0%) male patients. Although severe vitamin D deficiency was not detected in healthy men, two healthy menopausal women using proton pump inhibitor had severe vitamin D deficiency. In the healthy group, vitamin D levels were within normal limits in five women and six men, while in the patient group, only one woman and one man had normal vitamin D levels. The magnesium level was normal in all participants except two patients who received a proton pump inhibitor.

In our 12 patients who required warfarin at a daily dose of 10 mg or more to obtained targeted INR values, targeted values were maintained at lower doses of warfarin by eliminating vitamin D deficiency.

Although not planned in this study, heterozygous Factor V Leiden (FVL) mutation was detected in 25 of DVT patients (12 males and 13 females) in another ongoing study. Furthermore, all patients with FVL mutation had severe vitamin D deficiency (ranging from 3.1 to 9.2 ng/mL).

DISCUSSION

Vitamin D has recently been found to be an immunomodulator that might exhibit an antithrombotic effect [9]. Some studies found an association between low vitamin D levels and VTE [10,11]. It has been speculated that changes in vitamin D status may be a possible cause of seasonal changes in thromboembolic diseases such as DVT [10]. Thus, we conducted our study during the cold autumn and winter months in order to avoid seasonal changes.

Vitamin D, derived from sunlight exposure or nutrients, is not biologically active. Thus, vitamin D should be converted into its active form (1,25(OH)2D); calcitriol). During this conversion, hydroxylation should take place twice. The first hydroxylation happens in the liver by the 25-hydroxylase to convert vitamin D to 25(OH)D. The second hydroxylation occurs in the kidneys by the 1 alpha hydroxylase to generate 25(OH)2D [12,13]. The various stages of vitamin D transformations to generate this active form are associated with the presence of magnesium [14]. Furthermore, it has also been reported that magnesium could determine the number of vitamin D receptors (VDRs). Thus, optimal benefits of both exogeneous and endogenous vitamin D may be obtained with adequate magnesium availability [14]. Fortunately, industrial agriculture in our region is underdeveloped. Therefore, magnesium deficiency was not found in our series except two patients using proton pump inhibitor.

Table 1: Demographics and mean vitamin D levels of the participants.

	Female Patients	Male Patients	Healthy females	Healthy males
Number of participants	40 (48.8%)	42 (51.2%)	39 (56.5%)	30 (43.5%)
Age distribution of patients (mean±SD)	18-89 (55.31±18.58)	23-89 (58.19±15.31)	20-86 (53.28±18.42)	21-86 (54.27±18.35)
Vitamin D levels (mean±SD) (ng/mL)	3-31.5 (11.91±7.56)	5.05-24.1 (13.24±5.29)	3-44.7 (18.11±9.32)	10-48.90 (19.89±8.29)
No. of patients with deficien8t vitamin D level	36 (90%)	32 (76.2%)	19 (48.7%)	15 (50%)
No. of patients with sufficient vitamin D level	1 (2.5%)	1 (2.38%)	5 (12.8%)	6 (20%)

Calcitriol has also been recognized as a hormone because its metabolic function is mediated by VDR in cells [15]. VDR specifically binds calcitriol [15]. This vitamin D/VDR system has a key role in maintaining normal antithrombotic function in vivo [16]. VDR activation may possibly suppress thrombogenicity due to its physiological role in maintaining antithrombotic homeostasis [3]. Based on these studies, we might suggest that vitamin D deficiency contributes to the formation of venous thrombosis.

The risk of VTE is greatest if the inherited and environmental risk factors contributing to the development of VTE are combined [17]. FVL mutation is a well-known thrombophilic risk factor that increases the risk of DVT. However, the majority of FVL carriers do not develop DVT [18]. In this study, severe vitamin D deficiency was detected in all DVT patients carrying FVL mutation, suggesting that a combination of FVL mutation and acquired risk factors such as vitamin D deficiency may lead to a greater risk of DVT.

The active form and potent analogues of vitamin D exhibit anticoagulant effects by up-regulating the expression of thrombomodulin and reducing the expression of tissue factor [19,20]. Coagulation is promoted due to inflammatory mediators by increasing tissue factor production [21]. Besides, vitamin D could be directly or indirectly acting on the coagulant marker [22]. Vitamin D also have a possible role in maintaining the integrity of the vascular endothelium [10]. If vascular wall damage occurs, subendothelial tissue factor is exposed to blood and binds plasma factor VIIa, and a series of reactions are initiated that lead to thrombosis [23].

Vitamin D deficiency in diabetic patients may impair the condition of the disease and result in more complications such as the promotion of thrombosis [4]. Administration of vitamin D improves endothelial function in diabetics with vitamin D insufficiency [24]. Therefore, we excluded diabetics, as there may be an association between diabetes mellitus and vitamin D deficiency.

In a Swedish female cohort, Lindovist et al. 10), reported that sunlight reduced VTE risk by 30% and even risk was 50% lower in summer than in winter. Vitamin D deficiency has been reported to increase the risk of VTE in those with spinal cord injuries [25]. Furthermore, significantly lower vitamin D levels have been found in stroke patients with DVT [26]. In an Iranian study conducted by Dehghani et al. [1], vitamin D deficiency was found to be 71.4% in VTE group and 42.9% in healthy controls. Similarly, vitamin D deficiency was detected to be 82.9% in the patients and 49.7% in the controls in our series. As can be seen, vitamin D deficiency is common even in healthy subjects.

In a study conducted in the healthy Turkish population, 25(OH)D levels were 21.0±9.3 ng/mL in males and 18.2±11.2 ng/mL in females [27]. Similarly, in this series, the mean 25(OH) D level was 19.89±8.29 ng/mL in healthy men and 18.11±9.32 ng/mL in healthy women. However, the mean 25(OH)D levels were significantly reduced in both female patients (11,91±7.56 ng/mL) and male patients (13.24±5.29) compared to healthy counterparts (Table 1). Our finding suggests that vitamin D deficiency increases the risk of deep vein thrombosis in the Turkish population. In contrast, Folsom et al. [8], have not detected a significant relationship between low vitamin D levels and the incidence of VTE over a twenty-year follow-up. Furthermore, it has been reported that vitamin D administration does not have a protective effect on the risk of venous thrombosis [28]. We estimate that racial and regional differences are likely to play a role in these differences.

In patients with low vitamin D concentrations, a combination of vitamin D and warfarin treatment has continued targeting INR levels in lower doses of warfarin, so vitamin D may have anticoagulant properties [29]. Similar results were obtained in our12 patients using warfarin. Therefore, vitamin D may have a significant contribution in reducing the risk of recurrences of DVT after discontinuation of anticoagulation therapy.

In a study conducted in Switzerland, it was reported that the risk of COVID-19 disease has a stronger association with the 25 (OH) D concentrations, rather than other respiratory infection [30]. Therefore, in the still spreading COVID-19 epidemic, everyone, especially FVL carriers, should avoid vitamin D deficiency.

Hospitalized COVID-19 patients have an increased risk of developing DVT due to endothelial damage, immobility, and immune reactions that trigger prothrombotic changes [31]. Moreover, VTE has been reported to complicate the clinical course of inpatients with COVID-19, even with thromboprophylaxis [32]. The risk of vitamin D deficiency continues to increase due to the lockdown implemented due to the COVID-19 outbreak, which has not yet lost its effect. Since it has also been advocated that increasing vitamin D levels in COVID-19 patients may be beneficial [33], in those with low vitamin D levels, supplementation may not only reduce the risk of VTE, but may also contribute prophylaxis and treatment of COVID-19. Since DVT has been reported to be considered a relatively common and potentially fatal complication of COVID-19 [34], it is important to avoid low vitamin D concentrations, especially during the current pandemic.

CONCLUSION

Our study supports the view that there may be a relationship between DVT and low vitamin D levels. Although the number of patients is not sufficient, we assume that severe vitamin D deficiency may be a risk factor to be considered for DVT, especially in FVL carriers. However, our findings should be supported with further studies.

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