

Augmentation of anticoagulant effect with vitamin D: possible therapeutic target for venous thromboembolism

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Abstract

Venous thromboembolism is a leading cause of morbidity and mortality especially in the elderly. Arrays of risk factors altering the blood flow, endothelial function and coagulability have been identified. However, the precise mechanisms that trigger clotting in major veins have not been fully elucidated. Activation of endothelial cells by hypoxia or inflammatory stimuli results in surface expression of adhesion molecules that facilitate the binding of circulating leukocytes and microvesicles. Subsequent leukocyte activation induces the release of potent procoagulant tissue factor that triggers thrombosis. Aging, immobility, smoking, surgery, OCP intake, cancer etc predispose to stasis, increased coagulation factor levels, impaired function of the venous valves, decreases in the efficacy of natural anticoagulants associated with the vessel wall, increased risk of immobilization and increased risk of severe infection. Prophylaxis is both mechanical and pharmacological with anticoagulation being the mainstay of treatment. Thus, better understanding the mechanisms of venous thrombosis may lead to the development of new therapeutic / preventive modalities. Recently, vitamin D, the sunshine hormone, has been in the limelight due to some experimental and epidemiological evidences showing its antithrombotic actions by various mechanisms. With emerging data about the potential association of vitamin D as an antithrombotic agent, our review has dissected the recent evidences of vitamin D having any beneficial effect on the markers of thrombosis or improvement among patients with deep vein thrombosis/pulmonary embolism(DVT/PE).

Keywords: Venous thromboembolism; Deep vein thrombosis; Vitamin D.

Introduction

Deep vein thrombosis (DVT) is a potentially dangerous condition with a myriad of risk factors. The pathophysiology of DVT was described by Virchow in 1846 as a triad that includes changes in the vessel wall (injury), changes in the pattern of blood flow (venous stasis), and changes in the constituency of blood (hypercoagulability). Pulmonary thromboembolism is a deadly complication of venous thrombosis and the leading cause of preventable hospital mortality. Another problem associated with vascular clots is post-thrombotic syndrome (PTS) which eventually becomes a chronic burden on both the patient and health care system. This complication, caused by residual venous

abnormalities after a resolved DVE, includes chronic leg pain, swelling, dermatitis, and leg ulcers. Post-thrombotic syndrome hampers the quality of life along with considerable adverse economic effects. Deep vein thrombosis frequently occurs in bedridden aged, post surgical, coronary artery disease (CAD) and cancer patients. Smoking, intake of oral contraceptive pills, prolonged sitting like driving or flying etc increase the incidence of deep vein thrombosis [1,2]. The mainstay of treatment is anticoagulant therapy. Low-molecular-weight heparin, unfractionated heparin, and vitamin K antagonists are the treatment of choice. Prophylaxis is very important and can be mechanical and pharmacological. Currently newer anticoagulants specifically targeting components of the common pathway have been recommended for prophylaxis. These include fondaparinux, a selective indirect factor Xa inhibitor and the new oral selective direct thrombin inhibitors (dabigatran) and selective factor Xa inhibitors (rivaroxaban and apixaban). Others are currently undergoing trials. Thrombolytics and vena caval filters are very rarely indicated in special circumstances [3]. However, hemorrhagic complications are the most common adverse effects of anticoagulant therapy. Anticoagulation therapy for 3-6 months results in major bleeding complications in 3-10% of patients [4]. High-risk populations (> 65 y with a history of stroke, GI bleed, renal insufficiency, or diabetes) have a 5-23% risk of having major hemorrhage after 90 days. Patients who require year long or indefinite anticoagulation (because of chronic risk factors) have double the risk of hemorrhage [5]. Significant bleeding (ie, hematemesis, hematuria, GI hemorrhage) should be thoroughly investigated because anticoagulant therapy may unmask a preexisting disease (eg, cancer, peptic ulcer disease, arteriovenous malformation). Vitamin D is a steroid hormone whose deficiency is mostly seen in diseases such as cardiovascular diseases, neurodegenerative diseases, diabetes mellitus etc [6,7]. Fewer studies have also observed a vital role of this vitamin with DVT. Thus, this mini review attempts to explore the multiple mechanisms of DVT pathogenesis along with the recent emergence of vitamin D as a potential candidate for preventive and therapeutic strategies of DVT.

Molecular mechanisms of DVT

Molecular mechanisms involving thrombotic events employ endothelial dysfunction and inflammation as major role players in the pathogenesis of thrombosis. However, except for thrombosis after surgery, examination of thrombus in majority of DVT fails to show any evidence of obvious endothelial injury [8]. Blood is flown back from the venous system of the lower limbs to the heart by the calf muscles in the legs acting as pumps. In addition, valves in the large veins prevent reflux of the blood. Venous thrombosis is believed to originate at the venous valves [9]. These are also the areas where stasis and hypoxia may occur. Furthermore, venous stasis induced in animal models has revealed that oxygen tension drops very rapidly once blood flow is halted [10]. It has also been seen that natural anticoagulant proteins are highly expressed at these valve areas compared to other parts of the vessel walls. Moreover, the inter individual variation in the regional distribution of the antithrombotic proteins like thrombomodulin and endothelial protein C receptor (EPCR) in the valve or venous sinuses also influences the initiation of thrombosis arising out of stasis, one of the most important factors of Virchow's triad [11]. In addition, hypoxia can lead to up-regulation of procoagulant activity including tissue factor release on endothelium [12,13]. Acute stress or inflammation causes interleukin and C-reactive protein (CRP) production which in turn can increase the procoagulant activity of tissue factor (TF), a potent initiator of the extrinsic coagulation pathway 75-fold and thereby lead to thrombosis [13]. On the other hand, P-selectin, an adhesion molecule that can contribute to cell-cell interactions, and PSGL-1, a major ligand for P-selectin also play an important role in thrombus formation. Tissue factor and P-selectin both are necessary for thrombus formation and appear to both be resident on microparticles derived from monocytes [14,15]. On the contrary, another study in mice model has shown that tissue factor is drastically reduced in blood cells in DVT mice, indicating that the source being endothelial wall [16]. Secondly, increased levels of coagulation factors, particularly factor VIII, von Willebrand factor, factor VII and prothrombin are associated with an increased risk of thrombosis [17]. Obese individuals have increased levels of coagulation factor VIII and IX possibly contributing to the increased risk of thrombosis, but the risk associated with obesity remains even after adjustment for clotting factor levels [18]. Hence it is plausible that other factors like tissue inflammation may also be operating as a contributory factor in thrombosis. Interestingly, a recent meta-analysis of 8 observational studies concluded that statins reduce the risk of venous thromboembolism (VTE) [19]. Moreover, aging is the strongest risk factor for thrombosis due to decrease in natural anticoagulants like protein C, persistent activation of a procoagulant state (prothrombin fragment, D dimer) or inflammation associated changes in vessel wall [20]. The actual mechanisms are still controversial. Exact mechanisms for prothrombotic state with aging should be identified which can aid in future therapeutic strategies for prevention and management of thrombosis.

Vitamin D deficiency and DVT

Recent literature survey highlights the association of vitamin D deficiency with DVT. The possible relationship between vitamin D and thrombosis emerged when a seasonal variation was observed in the risk of venous thromboembolism. A cohort study by Lindquist, et al observed the extent of sun exposure and risk of developing VTE in 29518 women who were followed up for 11 years and it was seen that the risk of VTE was 30% lower in women who had an adequate sun exposure and the risk for developing VTE was highest in winter and the lowest in summer [21]. Vitamin D deficiency has also been demonstrated in another cohort study, in which lower vitamin D level was associated with an increase in ischemic heart disease, myocardial infarction, and early death at 29 year follow-up [22].

Several epidemiological studies have estimated that vitamin D3 deficiency or insufficiency is an extremely common condition among adults in western as well as other countries. Although there is no consensus on the optimal levels of 25(OH)D, vitamin D3 deficiency has been defined by most experts as a serum 25(OH)D level of less than 20 ng/mL (<50 nmol/L) for the general population [23,24]. A rapidly evolving knowledge base indicates that vitamin D3 deficiency is much more prevalent than it was presumed to be decades ago. Further, it has been well established that apart from maintaining skeletal health and calcium balance, this hormone exerts a lot of extraskeletal actions on various target tissues and organs. Vitamin D has got anti-inflammatory, anti-oxidant and immunomodulatory effects on brain, heart and other organs as well [6]. Besides, it also has some anticoagulant properties which have been proved by some studies. Likewise, in a placebo-controlled randomized trial of the high-dose calcitriol (the active form of vitamin D) conducted by Beer et al, a significantly lower numbers of thrombotic events occurred in cancer patients compared to placebo controls, suggesting that vitamin D is an antithrombotic agent [25]. A study by Koyama et al found that 1,25(OH)2D exerts anticoagulant effects by upregulating the expression of an anticoagulant glycoprotein, thrombomodulin, and downregulating the expression of a critical coagulation factor, tissue factor, in monocytic cells, including human peripheral monocytes [26]. Although some inconsistent data still exist, several cell culture and animal studies also demonstrated that 1,25 (OH)2D and its synthetic analogs downregulates the expression of type-B natriuretic peptide and play an important role in cell proliferation/differentiation, regulation of the immune system, as well as modulation of vessel relaxation and endothelial regeneration through the regulation of type B-endothelin receptor, oxytocin receptor, and prostaglandin endoperoxide synthase-1 [27]. To clarify whether VDR activation could also play any antithrombotic actions in vivo, Aihara et al found that VDRKO mice displayed a phenotype of increased thrombogenic activity. ADP-induced platelet aggregation was enhanced in normocalcemic VDRKO mice compared with wild-type and hypocalcemic VDRKO mice [28].

Although several studies have been conducted regarding this subject, data from human studies are less conclusive than in vitro

or animal studies. Ngo et al reported that lower levels of 25(OH) D were associated with increased plasma hs-CRP and asymmetric dimethylarginine concentrations, a marker of endothelial dysfunction, in a normal population cohort of 253 individuals aged 51 to 77 years [29]. In line with these observations, Jorde et al reported that there were significant inverse associations between 25(OH)D and tPA and PAI-1 antigen levels, and between 1,25(OH)2D and tPA and hs-CRP levels in 206 healthy individuals [30]. A recent pilot randomized clinical trial was done on 40 vitamin D-deficient patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) by Hejazi et al. The intervention group received an oral dose of 50,000 IU vitamin D3 every week for 8 weeks, followed by once every 2 weeks for 4 weeks for a total of 3 months, while the control group did not receive vitamin D. Treatment of vitamin D deficiency had no significant effect on hs-CRP or P-selectin after 3 months among DVT/PE patients. However, treatment of vitamin D deficiency in these patients resulted in the control of the international normalized ratio (INR) with lower doses of warfarin [31]. This observation is the first clinical report of enhancement of the anticoagulant effect of warfarin by the supplementing of vitamin D. One previous study also observed a higher prevalence of vitamin D deficiency among DVT/PE subjects, but no significant association was found between vitamin D levels and hs-CRP or P-selectin [32]. Thus, larger clinical trials are very much essential to clarify the effect of vitamin D deficiency on thrombosis.

Vitamin D in CVD

It has been suggested that venous thromboembolism and CAD are not entirely separate problem but are linked in terms of the risk factors like smoking, obesity, female sex etc. However there are inconsistent findings among few studies regarding this aspect. Vitamin D deficiency accelerates cardiovascular morbidities through inflammatory pathways, insulin resistance, beta-cell dysfunction and activation of renin-angiotensin-aldosterone system [33]. One study by Takeda et al demonstrated that an orally administered active form of vitamin D3 (calcitriol) in mice led to a marked reduction in atherosclerotic lesion formation. No significant associations were found between prothrombin fragment 1 p 2, factor VII coagulant activity and vitamin D3 levels [34]. A recent meta-analysis including 17 prospective cohort studies and randomized trials observed that moderate to high doses of vitamin D supplementation may reduce the risk for cardiovascular disease, with benefits mainly seen in patients receiving dialysis [35]. However, A systematic review of 13 observational studies examining the association of vitamin D status with cardiometabolic outcomes (type 2 diabetes, hypertension, or cardiovascular disease) concluded that the association is uncertain and the results were hampered by the heterogeneity of studies [36]. Moreover, the DIABHYCAR trial has shown that genetic/ haplotype variations in vitamin D receptor genes might be associated with an increased risk of CAD among diabetic patients [37].

Discussion

Presently research on novel anticoagulant drug development

is centering around agents that are able to target various stages of the coagulation cascade. Drugs under investigation that act in the initiation phase include tissue factor pathway inhibitors (TFPIs) and nematode anticoagulant peptide (NAPc2). Drugs acting on the third stage i.e. the thrombin activity phase, are now established as the direct thrombin inhibitors and are in use. A partial listing of these emerging new anticoagulants includes razaxaban, idraparinux, bivalirudin, lepirudin, and ximelagatran. The role of vitamin D supplementation in prevention of the initiating events of thrombosis eg, inflammation, leucocyte dysfunction, endothelial integrity are the prime focus now and exploration is necessary in animal based studies as well as human trials. The recent pilot study indicating the augmentation of anticoagulant effect of warfarin along with vitamin D supplementation [hejazi et al] sheds some hint in this context. Thus, role of vitamin D supplementation in DVT patients should be explored further by large scale trials with standardization of dose and duration and correlation with anticoagulant therapy. Augmentation of currently available anticoagulant action by vitamin D may lower their dosing thereby decreasing the hemorrhagic complications of anticoagulation therapy.

While epidemiology has identified fundamental risk factors which increase the propensity to develop venous thromboembolism, we still lack the knowledge of the basis for the initiation of thrombosis, how exactly the valves are involved in the process and what specific factors are altered with advancing age that contribute so markedly elevated risk of thrombotic events. Even though growing molecular evidences indicating a role for vitamin D as an anti-inflammatory and anticoagulant agent are strong, results from clinical trials regarding vitamin D and thrombosis are still inconclusive. There can be several reasons for this discrepancy including the differences in the setting, design, population, supplementing dose of vitamin D, and follow-up period of these trials. Secondly, the important role of genetics should not be overlooked, as genetic differences exist in both vitamin D receptor genes and inflammatory factor genes. Large trials need to be conducted in similar populations to minimize the role of genetic variability. Thirdly, vitamin D acts as a nuclear transcription factor, and its function may be observed in long-time follow-up periods. Taken together, larger clinical trials and meta-analysis studies are still needed to clearly show the effect of vitamin D supplementation in thrombosis. Food sources of this pivotal nutrient are not as abundant as other vitamins and a normal diet may not fulfill daily recommended amounts of vitamin D. Therefore, adequate exposure to sunlight and using vitamin D supplementations would be a good choice.

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