

Can vitamin K synthesis altered by dysbiosis of microbiota be blamed in the etiopathogenesis of venous thrombosis?

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Venous thrombosis (deep vein thrombosis and pulmonary embolism) is seen in one out of 1,000 individuals in the general adult population [1]. However, as age advances, this rate goes up to one in 100 individuals, and the mortality rate stands at 30% [1]. If the etiopathogenesis of thrombosis can be clarified, the rate of morbidity and mortality can be reduced. Currently, the etiopathogenesis of thrombosis is explained by Virchow's triad [2], which includes (i): changes in blood flow (deceleration of blood flow leads to the impairment of laminar blood flow; being overweight, being bedbound, having congestive heart failure and age-related alterations), (ii): changes in vessel walls (conditions arising from traumas and inflammatory and degenerative diseases), and (iii): coagulation abnormalities [congenital hypercoagulation (protein C, S, and antithrombin III deficiency)] and acquired hypercoagulation (oral contraceptive, pregnancy, nephrotic syndrome, systemic lupus erythematosus, inflammatory intestinal disease, malignancies, and their treatment) [2, 3]. Although changes in blood flow and vessel walls play major roles in the etiopathogenesis of thrombosis, coagulation abnormalities appear to figure more prominently in the underlying mechanism of the disease [3]. Of the natural anticoagulants synthesized in the liver, proteins C and S have to go through a carboxylation process involving vitamin K [4]. Therefore, vitamin K, a fat-soluble essential vitamin, plays a key role in maintaining normal coagulation. Beans, green tea, olives, olive oil, leafy green vegetables like spinach, broccoli, Brussels sprouts, asparagus, cabbage, cauliflower, green

peas, soybean seeds, meat (beef liver), eggs, grains, and dairy products are rich in vitamin K [5, 6]. About 80 to 85% of vitamin K is absorbed by the terminal ileum [7]. The other the major source of vitamin K aside from the diet is microbiota, a newly recognized organ in the body [7]. Skin and the gastrointestinal system are the primary locations of the microbiota. The gastrointestinal system is inhabited by over 100 trillion bacteria. There is a delicate balance between the host and microbiota based on good-neighborliness [8]. However, a number of factors including dietary habits, use of antibiotics and chemotherapeutics (5-fluorouracil over 5 µg/ml prevents the reproduction of bacteria), and personal hygiene bring about changes in the populations of the microbiota [9]. To illustrate, several forms of vitamin K (menaquinones) are synthesized by *Bacteroides*, *Enterobacter*, *Veillonella*, and *Eubacterium lentum*, which are the usual members of the microbiota (intestinal microflora). Dysbiosis, or impairment of the normal composition of the microbiota, has been reported to be associated with many diseases, including cancer and inflammatory intestinal diseases [7, 8]. If the number of vitamin K-synthesizing bacteria in the microbiota increases for any reason (or decreases to reduce vitamin K synthesis as a compensatory mechanism), vitamin K levels will be elevated (even if dietary vitamin K intake is restricted) and venous thrombosis will occur. One reason why we cannot elevate the international normalized ratio despite Coumadin administration in certain cases may be that the excessive vitamin K synthesized by the microbiota can be absorbed more than usual along the intestinal lymph vessels together with lipids and thus affect the coagulation cascade [5]. Consequently, an overall evaluation of the information above indicates that when the doses of anticoagulation medications are to be decided, the possible role of the members of the microbiota in the development of venous thrombosis and whether there is an increase in the amount of vitamin K-synthesizing bacteria should be analyzed [7]. In this

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way, even after the prevention of venous thrombosis, healthy microbiota transplantation can be performed, if necessary, to impede vitamin K of microbial origin. Given that the role of the microbiota in the development of venous thrombosis has not been studied yet, it can be anticipated that by analyzing the amount of vitamin K originating from the microbiota, mortality associated with venous thrombosis can be reduced.

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