On elucidating a possible link between vitamin D and venous thromboembolism – Finding a piece of the puzzle

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Venous thromboembolism (VTE) is one of the most common cardiovascular diseases affecting women. It increases its incidence with age, rising from 0.4% yearly in the thirties, to 1% yearly at around age 50 and reaching 2% at 65 years of age (1). The risk factors for VTE include thrombophilia, immobilisation, surgery, cancer, overweight, pregnancy, combined oral contraceptives, familial thrombosis, and a prior anamnesis of a VTE. Women with an anamnesis of VTE have a yearly 10- to 20-fold increased risk above the mean of recurrence, ranging from approximately 1% yearly at 30 years of age to about 8% at 60 (2-4).

In this issue of Thrombosis and Haemostasis, Brodin et al. (5) publish a paper entitled “Serum levels of vitamin D are not associated with future risk of venous thromboembolism. The Tromsø Study”. In this Editorial, I will briefly sketch some background information and discuss clinical implications of a possible link between vitamin D and VTE.

There is conflicting epidemiological evidence in retrospective studies of seasonal variations in the risk of VTE (6-8). The mechanisms for an increased risk of VTE in the wintertime have been speculated upon have been vasoconstriction due to cold and reduced physical activity (6). In 2011 we published data from the MESS study, a large prospective cohort of South Swedish women, where we not only found an increased risk of VTE during winter, but also that women with active sun exposure habits were at lower risk of VTE compared to those who avoided sun exposure (9).

Women with active sun exposure habits have higher vitamin D levels and lower risk of vitamin D deficiency (10). Thus, a novel etiological mechanism involved in the pathogenesis of VTE suggested itself. As it was an observational study, our findings were of the hypothesis generating type and not proof of a causal relationship.

Alternative explanations include that the protective effect may have been due to the following: (i) Improving vitamin D status which lowered the risk of VTE. This could be further subdivided into either an inverse relationship between VTE and vitamin D levels or an avoidance of vitamin D deficiency may be related to lowering the risk; (ii) Exposure to additional sunlight would affect the melatonin system; (iii) Cold weather has been implicated. With more hours of sunlight there will be less cold weather and improved vitamin D status; and (iv) The association between active sun exposure habits and lower risk of VTE might be the result of a bias that has not been adjusted for in the analysis. Active sun exposure habits are almost impossible to distinguish from a healthier lifestyle.

The study of Brodin et al. gives epidemiological evidence that increasing vitamin D levels do not decrease VTE risk in Norway (5). Although not significant in the Brodin study, the risk of the highest quartile (25-OH vitamin D > 70 nmol/l) compared to the lowest quartile (25-OH vitamin D < 44 nmol/l) showed an adjusted odds ratio of 0.76 (0.45-1.28). Thus, as the authors mention, the study’s results might not be generalisable to those with vitamin D deficiency. If the latter is the true mechanism, this might explain the heterogeneity in results as depending on the incidence of vitamin D deficiency in the studied population. Despite being located at comparable latitude or even more northerly than Sweden, Norway’s vitamin D levels seem to be considerably higher (mean 25-OH vitamin D 58 nmol/l) than Sweden’s. Data (n = 120) from a subgroup of our pregnant women in winter and spring showed that none were at sufficient levels (>75 nmol/L), and more than 50% were at deficient levels (< 50 nmol/L). The mean vitamin D value was 10 nmol/l lower than the Norwegian levels (non-published data). This might be due to a diet including high fish or fish liver oil consumption, as indicated by the authors, or to the fact that women seem to be at an increased risk of vitamin D deficiency compared to men (5, 11).

Might further knowledge of the relation between VTE and vitamin D/sun exposure be clinically useful?

Half of all VTEs are reported to occur during high-risk periods and half during low-risk periods (12). During such high-risk periods as surgery or pregnancy, medical thromboprophylaxis might lower the risk of VTE among those who are at high risk according to guidelines. In low-risk periods, however, medical thromboprophylaxis is usually not recommended and lifestyle advice might be an effective alternative.

Not smoking, watching one’s weight, and exercising are effective in lowering the risk (1, 13, 14). There are also reports that consuming coffee or wine in moderation is associated with a lower risk of VTE, as compared to those who abstain or consume a great deal of coffee or wine (15, 16). The determination of a causal relationship for sufficient vitamin D/active sun exposure habits could be of great importance in reducing the risk of VTE during low-risk periods, and also for optimising therapy during high-risk periods for all those patients at increased risk.

Do women care about lifestyle advice?

We carried out a survey of factor V Leiden (FVL) carriers, i.e. women at increased risk of VTE, by means of a questionnaire in a
large cohort (17). Many of these women informed us that after they became aware that they were FVL carriers, they began to exercise more, eat healthier, and 84% of those taking combined oral contraceptives changed the method of contraception. These women at increased risk of VTE asked for more life-style advice in order to keep their risk low. Thus, women at high risk appear to be rational and highly motivated to change their habits.

What is the possible link between vitamin D deficiency and VTE?

It has been suggested an up-regulation of tissue factor and inflammation and a down-regulation of thrombomodulin occurs in relation to vitamin D deficiency (18). In an animal model, active vitamin D was effective in avoiding disseminated intravascular coagulation (DIC) after lipopolysaccharide stimulation (19). A large 1958 British Birth Cohort study found that vitamin D levels were inversely related to tissue plasminogen activator (11). The authors cited above stated that vitamin D status might be important for maintaining antithrombotic haemostasis (11). Recent laboratory evidence has shown that vitamin D deficiency was related to increased D-imer and increased mean platelet volume (20). The latter has been proposed as a marker of platelet reactivity and cardiovascular risk.

From an evolutionary perspective there must have been an advantage to having less pigmented skin in order for depigmentation to evolve as man started to migrate away from the equator. Strong evolutionary forces have probably caused these changes to take place. Different advantages are possible, but avoiding vitamin D deficiency is one attractive candidate. In comparison to a black man from Africa, a fair-skinned Caucasian needs to be out in the sun only one-sixth of the time to produce the same amount of vitamin D (21). American Africans have been reported to be at 60% increased risk of VTE, as compared to whites (22). Reproduction has to be involved in this evolutionary advantage and it is not unlikely that cardiovascular diseases including VTE also are dependent on sun/vitamin D (23).

Future research should be directed to elucidate the relationship between vitamin D deficiency and VTE, which can be most efficiently done in populations with a high incidence of vitamin D deficiency, and, since women appear to be at increased risk of vitamin D deficiency, preferably in a population of women. If vitamin D supplementation can be shown to be an effective measure it might be a lot easier than keeping one’s normal weight and exercising.

Of note, there appears to be considerable increase in patient demand for lifestyle advice. In addition, there would be a great clinical usefulness if a link between VTE and vitamin D could be established. Further, there are plausible laboratory and evolutionary data supporting the most promising mechanism at present as a means of lowering VTE risk, avoidance of vitamin D deficiency. Brodin et al. have delivered a piece to this puzzle in showing that increasing vitamin D levels from normal or high does not lower VTE risk.

Conflicts of interest

None declared.

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