Diet and Cardiovascular Disease: Venous Thrombo-embolism

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Abstract

Venous thromboembolism is responsible for considerable morbidity and mortality. It is estimated to be the second most common medical complication, the second most common cause of excess length of hospital stay, and the third most common cause of excess mortality. Recurrences are common. Anticoagulation is usually given for three months. However, inefficiency and major bleeding is often noted. External compression devices and balloon or direct thrombectomy and insertion of inferior vena cava filters are also available. Increasing data indicate that diet may play an important role in preventing venous thromboembolism. Obesity, which is significantly related to diet, may contribute to 30% of all venous thromboembolism cases. Further, plant-based diets, such as the Mediterranean, prudent, and the Dietary Approaches to Stop Hypertension diets are related to a lower incidence of venous thromboembolism. This manuscript reviews the published literature on the relationship of various dietary components and dietary patterns, and their impact on the development and progression of venous thromboembolism.

Keywords: diet, cardiovascular disease, venous thromboembolism, deep vein thrombosis, plant-based diet, red meat

Introduction

Venous thromboembolism (VTE) denotes both deep vein thrombosis (DVT)), and pulmonary embolism (PE)[1,2]. It is a major preventable and treatable cause of morbidity and mortality in hospitalized patients[3,4]. It has an incidence rate > 100 per 100,000 person-years[5]. The first manifestation of VTE is often fatal PE[6]. It can be responsible for up to 10% of all in-hospital mortality[6,7]. VTE can be provoked (60% to 75% of cases) by strong triggering or persistent risk factors[8-10] or unprovoked or idiopathic (25%-40% of cases) in nature[11,12]. The former is usually associated with trauma, cancer, pregnancy, long-term immobilization, obesity, or surgery, while the latter often occurs without warning or identifiable causes, and often outside of a medical setting. Lifestyle factors, including diet, are contributors to VTE[13].

Venous thromboembolism is not a benign disease[14,15]. It is estimated to be the second most common medical complication, the second most common cause of excess length of hospital stay, and the third most common cause of excess mortality[3]. More than half of the cases are provoked by hospitalization, and 24% of these are attributable to surgery[11]. VTE is a major cause of death[16,17]. It is estimated that in the US, an estimated 857,000 deaths from DVT, 370,000 from PE, and 52,000 with VTE deaths occur[9]. It is also estimated that >370,000 VTE-related deaths

occur in Europe[17]. Because VTE disproportionately affects older patients, it is expected that these estimates will increase in the future as the global population ages[3].

Recurrence is common[19-21]. They also face increased mortality[22,23]. The short-term mortality rate is approximately 25%[22,23]. There is an increased risk of recurrence of almost 10% per year for non- provoked VTE, with a case- fatality rate of 3.6% to 12%[24-26]. Recurrence, despite anticoagulation, may occur after major surgery, major trauma, acute illnesses such as heart failure or pneumonia or with active cancer. Overall, it is estimated that one-third of patients suffer recurrent VTE within 10 years[27,28]. Current guidelines recommend anticoagulation treatment for 3 months after VTE[29]. For patients with a provoked VTE, treatment is usually safely discontinued after three months[30]. However, for patients with unprovoked VTE, the optimal length of treatment is not clear[31,32]. These patients are also more prone to suffer from other cardiovascular events, and this incidence is higher than in the general population, without VTE[33].

It is recommended that patients with DVT should be initially treated with oral anticoagulants (including rivaroxaban, dabigatran, and apixaban), intravenous heparin in the hospital, or with subcutaneous low-molecular-weight heparin (LMWH) along with warfarin. However, anticoagulation is not completely safe - a recent meta-analysis indicated major and fatal bleeding rates of 1.8% and 0.2%, respectively. Elevation of the affected limb and application of warm compresses to the affected area also help. In patients where anticoagulation therapy is potentially harmful, external compression devices could be used for DVT prophylaxis and treatment. Surgical procedures include balloon or direct thrombectomy and insertion of inferior vena cava filters[34,35]. Despite these measures, individuals may face increasing morbidity due to post-thrombotic syndrome[36]. Symptoms include pain, swelling, and ulceration, and these can severely impact the patients' health quality of life[37]. VTE is associated with an increase in the disability-adjusted life years[5]. It also increases the healthcare burden[38], with hospitalization[39], especially readmissions, being the primary cost driver[40]. Virchow in 1856 suggested that venous thrombosis was the result of stasis, hypercoagulability, and endothelial dysfunction (commonly known as Virchow triad)[41]. Besides other lifestyles, diet can play an important role in mitigating these factors[42-49].

Discussion

The effect of diet on DVT/VTE susceptibility has been known since World War 2 when food rationing (high-complex-carbohydrate, low-fat diet) resulted in a lower incidence of DVT/VTE in parts of Europe[50,51]. A multitude of subsequent studies has suggested that obesity may contribute to 30% of all VTEs[52]. Further, data also suggests that higher intakes of fruits (such as Kiwi, blueberries, cantaloupe, cherries, apples, cranberries, acai fruit, dragon fruit, citrus fruits, grapes, raspberries, papaya, mango, pomegranate) and vegetables (variety of different colors: mushrooms, onions [white], carrots, pumpkin [orange], spinach, broccoli, brussels sprouts, collard greens [green], bell peppers [red],, etc,), alcohol, vitamin E, vitamin B6, and fiber are inversely associated with VTE risk[13]. On the other hand, a Western dietary pattern with high intakes of red and processed meat and trans fatty acids increases the VTE risk by about 11%[52]. Predominantly plant-based diets, such as the Mediterranean (MedD)[53] and the prudent diet[54]

appear to have protective effects on VTE. Dietary Approaches to Stop Hypertension diet (DASH) also appears to be somewhat helpful[55].

Obesity

Diet influences obesity[56-58]. Obesity (as defined by body mass index or BMI) is a well-established strong risk factor for VTE[56-58]. A BMI should ideally be between 18.5 kg/m² to 24.9 kg/m². A BMI of 25 kg/m² to 29,9 kg/m² is considered overweight, while at or >30 kg/m² is diagnosed as obese[59]. An elevated BMI has been identified as a risk factor for VTE in several observational population- based studies[60,61]. In the LITE (Longitudinal Investigation of Thromboembolism Etiology) study (a cohort of 20,914 individuals aged 45 and older without prior VT, a relationship with higher BMI and increased risk of unprovoked and provoked VTE was documented (Hazard Ratio [HR]=1.3)[62]. Gregson et al. analyzed data from the Emerging Risk Factors Collaboration (ERFC) and the UK Biobank studies and reported that a BMI >30 kg/m² consistently showed a positive, dose- response association with incidence of VTE63. The HR was 1.47 in the UKB study for incident VTE per 1- SD higher body mass[63]. In the ERFC study, the HR was 1.43 for fatal VTE per 1-SD higher body mass[63]. Mahmoodi et al. calculated that obesity almost doubled the risk of VTE[64]. It is estimated that obesity is responsible for 30% of all VTEs in the United States[65]. Abdominal obesity (with or without BMI calculated obesity) is associated with a higher incidence of VTE[66]. Abdominal obesity is ascertained by several anthropometric measurements[67]. Waist circumference (WC) should ideally be <102 cm in males and <88 cm in females when measured to the nearest 0.1 cm at the umbilical level in a standing position[68]. The waist-hip ratio is normally 0.85 or less for women and 0.9 or less for men[69]. Less commonly used is the waist-height ratio – this is calculated by dividing the WC by height[70]. A ratio > 0.5 is consistent with central obesity[70]. Borch et al. in a study with 222 incident VTE cases and a median 12.3 years' follow- up time, found that WC was a better indicator of a higher risk of VTE when compared to BMI[71]. Yuan et al. estimated that although the population- attributable risk due to elevated BMI was 12.4%, it was much higher for a high WC - 23.7%[72]. The causal relationship between obesity and VTE has been confirmed with Mendelian randomization studies[73,74]. Even patients with a diagnosis of being overweight (BMI 25 kg/m² to 29,9 kg/m²) show a higher risk for VTE (Odds Ratio=2.1)[75]. Besides pre-existing excess body weight, weight gain also increases the risk of VTE. The Tromsø Study (n=1,802, with 302 incident VTEs over a median of 6 years) found that a greater weight gain (7.5–40.0 kg) was associated with a 1.92- fold higher risk of VTE when compared with those with no or a moderate (0–7.4 kg) weight gain[76]. The harmful effect of weight gain on VTE was recently confirmed by the ARIC (Atherosclerosis Risk in Communities) study (9,710 participants with 529 incident VTEs over 9 years). This study found that a higher weight gain (>7.71 Kg) was associated with a 1.46-fold higher risk of incident VTE when compared with those whose weight gain was +1.81 to +1.36 kg[77].

Excess body weight is associated with venous stasis, venous damage, and varicosity[78]. It is also associated with increased activity of the coagulation cascade[79] and decreased activity of the fibrinolytic cascade[80] and inflammatory factors[81]. Further, obesity also contributes to other chronic conditions such as hypertension, diabetes, hyperlipidemia, and cancer that increase VTE

risk[82,83]. Excess body weight may be more detrimental to females when compared with males[84,85]. In a cohort study from the US National Hospital Discharge Survey, obese women had a greater risk of DVT than obese men[84]. In the all-female Nurses' Health Study, obesity tripled the risk of unprovoked PE[85].

Fruits and Vegetables/Wholegrains/Fiber

A higher intake of fruit and vegetables is well known to be associated with lower total and cause-specific mortality, including a reduction in cardiovascular deaths[86]. Although many studies have questioned the benefit of fruit and vegetable intake on VTE, data remains favorable for a higher intake of fruits and vegetables in protecting against VTE[87]. The Longitudinal Investigation of Thromboembolism Etiology study (prospective study over 12 years, 14,962 middle-aged adults) showed that there was a 27% to 53% reduction in the risk of VTE when eating >2.5 servings per day of fruit and vegetables was compared with eating <2.5 servings per day[88]. Bhoopat et al. reported (multivariate analysis) that eating fewer vegetables was associated with an odds ratio (OR) for venous thrombosis of 3.74[89]. Violi et al. reported an inverse association between fruit and vegetable consumption and VTE risk[90]. Yuan et al. observed an inverse between fruit and vegetable consumption and risk of pulmonary embolism[91]. Further, fruits and vegetable intake (rich in vitamin K) help improve anti-coagulation control[92,93]. Some evidence suggests that elevated cholesterol increases the risk of VTE[94]. Greatly increasing dietary fiber may help decrease cholesterol levels. Published data is, however, not strong on the VTE protective effects of a generous intake of whole grains or fiber[95].

Fish

The evidence linking fish consumption with a lower risk of cardiovascular disease is strong[96,97]. A recent meta-analysis including 11 prospective cohort and 8 case–control studies totaling 408,305 participants proved the existence of an inverse association between fish intake and risk of acute coronary syndrome[96]. A modest and inverse association between fish intake and cerebrovascular disease was also reported in another recent meta-analysis of 26 prospective cohort and 12 randomized trials totaling 794,000 participants[97]. A similar inverse relationship was noted between fish intake and VTE[95]. Lyn et al. found that eating ≥0.1 serving of fish per day (or ≥1 serving per week for quintiles 2 to 5) were associated with a 30% to 45% lower risk of VTE than eating <0.1 servings of fish per day[95]. The benefit is probably due to the omega-3 fatty acids content of fish[98]. Fish eaters also live a healthier lifestyle – they follow a healthier diet, spend more time exercising, and smoke less, and these may also influence the risk of VTE in this population. If these confounding factors are considered, the benefits of fish consumption on the risk of VTE are less significant[99].

Coffee/Tea/Chocolate

The data on coffee/tea/chocolate consumption and the risk of VTE is sparse. Lippi et al. reviewed three studies (two prospective and one case-control) and concluded that coffee intake in an amount ≥5 coffee cups per day may reduce VTE risk by 25%[100]. There was some suggestion that lower amounts of intake may increase the risk when compared to abstainers. Overall, the data is too limited to ascribe a definite connection.

Alcohol

The association between alcohol consumption and venous thromboembolism (VTE) risk has been investigated by various observational studies with inconsistent results. Low to moderate alcohol consumption has been associated with a decreased risk of arterial thrombosis[101]. The association between alcohol consumption and VTE risk also has been investigated by various observational studies. Some studies reported a reduced VTE risk associated with moderate alcohol intake[102,103]. Moderate alcohol consumption was also related to a lower risk of VTE in a 2013 study[104]. Moderate alcohol consumption might have antithrombotic effects[105-107], although it is unclear whether these reported effects are due to ethanol or other compounds[108]. A much more recent study did not find an inverse association[109].

Some researchers have reported a U-shaped relationship[104]. Dimmitt et al. reported that alcohol intake was associated with factor VII, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1)[110]. Mukamal et al. found that light-to-moderate alcohol intake was related to lower levels of coagulation factors, but higher consumption was related to impaired fibrinolytic potential, which implied a J- or U-shaped relationship between alcohol intake and hemostatic parameters[111]. However, Chen et al. failed to find a U-shaped association[112].

Several studies have reported no association between alcohol intake and VTE[113-116]. A meta-analysis, involving almost 400 thousand participants and more than 10 thousand patients with VTE from 10 prospective studies (14 cohorts), concluded that alcohol intake was not associated with the risk of VTE overall[112]. However, some studies have suggested that alcohol may have some protective effects against VTE in women[102,103,117]. There is also some indication that wine may have some VTE protective benefits. In a prospective cohort study including 26,662 individuals, Hansen-Krone et al. found that wine consumption appeared to lower the risk of VTE[118]. This was also seen in a recent study by Yuan et al. for wine consumption and deep vein thrombosis[119]. It is unclear if this benefit is from resveratrol, which is present in red wine[120].

Finally, some studies indicate that acute alcohol intoxication may raise the risk of VTE[121]. Heavy alcohol consumption may induce endothelial dysfunction[122] and influence coagulation, fibrinolysis, and platelet activities[123-126]. These actions may predispose individuals to thrombosis[127,128]. In addition, alcoholism is pro-inflammatory[129] and this activates coagulation, and coagulation modulates the inflammatory activity[130]. Overall, these alcohol-associated changes increase thrombus formation and the risk of VTE. Alcohol use has been associated with an increased risk of cancer[131], and injuries[132] and these increase the risk for VTE. A recent meta- analysis of 10 prospective studies with a total of 441,128 individuals and 10,221 VTE cases found no association of alcohol intake with VTE[112]. Overall, the relationship between alcohol intake and increased risk of VTE is unclear.

Red Meat/Saturated Fats

In a prospective study over 12 years, 14,962 middle-aged adults participating in the Atherosclerosis Risk in Communities study were followed up for incident VTE. Individuals consuming >1.5 servings of red and processed meat per day had a 2 times higher risk of developing VTE than those consuming <0.5 servings per day[95]. Unprocessed red and processed

red meats are high in saturated fatty acids, which have been shown to increase platelet aggregation[133]. Further, high intakes of unprocessed red and processed red meat consumption have been linked to increased risk of cancer and cardiovascular disease, both of which increase the risk of developing DVT[109].

Vitamins/Micronutrients

Lyn et al. found lower VTE risk with increasing dietary intake of vitamin B6, folate, and foods rich in these nutrients was associated with a lower VTE risk. They attributed this to their effect on homocysteine levels[95,134,135]. However, supplementation with these micronutrients does not reduce the risk of incident or recurrent VTE[136,137]. Vitamin E stands out as its supplementation has been shown to have anticoagulant effects[138,139]. The only study, however, that demonstrated a clinical effect was a randomized 10- year clinical trial that showed that 600 IU vitamin E every other day reduced VTE 21% compared with placebo in healthy women (Women's Health Study)[140]. Since this trial has not been replicated, vitamin E supplementation is not recommended at this time for the prevention of VTE. It has been noted in several studies that whole foods with vitamins and minerals are often beneficial while individual supplementation is not – likely due to synergistic effects occurring among foods and their nutritive and nonnutritive components[141].

Special Diets

Epidemiological evidence suggests that a diet with ample fruits and vegetables and little meat may substantially reduce the risk of VTE by favorably affecting serum markers of hemostasis and inflammation. The Western diet is characterized by more frequent intake of red/processed meat, saturated fat, refined grains, and sugar and low intakes of fish, fruit, and vegetables[142]. It is associated with a higher risk of DVT. The ARIC study reported that there was a 60% increased risk for VTE in individuals with high adherence to the Western diet pattern[95]. The MedD is characterized by a high intake of fruits, vegetables, legumes, monounsaturated fatty acids (essentially extra virgin olive oil), and a moderate intake of fish and wine[143]. People eating MedD have a low intake of meat – meat intake is associated with gut microbiota-related over-production of TMAO (trimethyl-amino-oxidase), that favors arterial thrombosis[144]. Further, an elevated FVIIc, FVIIIc, and vWF, which are related to increased risk of VTE incidence[145,146], and elevated FVIIIc, which is related to recurrence[147], are favorably influenced by the MedD[148]. In the Dutch component of the European Prospective Investigation into Cancer and Nutrition (cohort of 34,708 individuals, a 2- unit stronger MedD score was associated with 0.74- fold lower pulmonary embolism risk[53]. Dietary Approaches to Stop Hypertension dietary pattern, which lowers blood pressure, also benefits VTE. A recent cohort study found that high adherence to this diet (slightly modified) was associated with a lower risk of VTE in 30,137 women and 36,193 men followed up for 17.3 years[55]. The prudent diet had more vegetables, fruit, cooking/dressing oil, cereals and legumes, whole grains, nuts, rice/pasta, fish, low-fat dairy, poultry, and water[149]. Although the "prudent" diet shares many common characteristics with the MedD, it does not include olive oil and wine. A recent cohort study revealed that high adherence to the prudent dietary pattern was associated with a reduced risk of VTE in 14,818 middle-aged adults followed up for approximately 22 years[54]. The ARIC study reported a relative risk of

noncancer VTE over 12 years of follow- up for the highest versus lowest quintile of the prudent dietary pattern hazard ratio was 0.69[95].

Conclusion

Venous thromboembolism is an important vascular disease growing research suggesting that unhealthy lifestyle risk factors may cause a considerable proportion of unprovoked VTE. It is estimated that a reduction of obesity, physical inactivity, current smoking, and Western diet by 25% in the general population might reduce the incidence of unprovoked VTE by 12%. As noted earlier, obesity and a Western diet are the major modifiable risk factors. The protective role of plant-based is persuasive. The MedD and the prudent diet have favorable effects in lowering the incidence and recurrence of VTE.

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