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Research Article

Cardiovascular Risk Factors and Venous Thromboembolism: Is there a Connection?

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Keywords

- Cardiovascular risk factor
- Venous thrombosis

Abstract

Background: Arterial thrombosis and venous thrombosis are medical conditions with high levels of morbidity and mortality, especially in developed countries. It has not yet been established if these disorders have physiopathological mechanisms in common. Dyslipidemia, hypertension, diabetes mellitus, and smoking have been investigated as possible risk factors for these pathologies, although their impact on venous thrombosis remains unknown.

Subjects and methods: We studied a group of 453 patients, 201 with VTE, and 252 patients with CVD (cases of cardioembolic stroke were excluded). A control group consisting of 346 subjects with no history of arterial thrombotic disease, VTE or cancer was also included in the study. All patients and controls were evaluated for the presence of the following risk factors: hypertension; Diabetes mellitus; dyslipidemia; smoking.

Results: All the risk factors included in the present study (hypertension, diabetes mellitus, dyslipidemia, and smoking) were associated with elevated risk of Cardiovascular Diseases CVD. Patients with alterations in the lipid profile had a higher risk of Venous Thromboembolism VTE (OR: 1.62, 95%CI: 1.04-2.52, p= 0.03), whereas subjects who smoke presented twice the risk of venous thrombosis (OR: 2.28, 95%CI: 1.49-3.48, p=0.0001).

After adjusting for age and sex, when we compared the two patient groups and controls, the multivariable analysis showed that dyslipidemia was a risk factor for VTE (OR: 1.66, 95% CI: 1.06-2.61, p=0.027), and it was not related with CVD (OR: 1.29, 95% CI: 0.84-1.98, p: ns).

Conclusion: Arterial and venous thrombosis share common risk factors such as dyslipidemia, HTA, and smoking.

BACKGROUND

Traditionally, arterial thrombosis and venous thrombosis have been considered as two distinct pathophysiological entities. In recent years, however, a possible association between venous and arterial thrombosis has been studied. Endothelial injury, inflammatory markers, and impaired fibrinolysis play an important role in the physiopathology of these entities. On the other hand, venous and arterial thrombosis shares certain cardiovascular risk factors, such as obesity, diabetes mellitus, hypertension, and hypertriglyceridemia, although this is still a controversial aspect [1]. In addition, there are some clinical conditions that favor the development of both venous and arterial thrombosis, such as hyperhomocysteinemia, antiphospholipid syndrome (APS), paroxysmal nocturnal hemoglobinuria, infections, myeloproliferative disorders, or hormonal therapy [2,3].

Different studies have analyzed the risk of venous thrombosis in patients with arterial disease, while others have described the risk of arterial disease in patients with venous thrombosis. *Prandoni et al.* studied a group of 299 patients diagnosed with venous thrombosis who did not have symptomatic atherosclerosis. The authors report that the presence of carotid plaques in patients with unprovoked VTE compared with secondary VTE and controls yielded an odds ratio (OR) of 2.3 and 1.8, respectively [4]. Later, the same researchers reported on a prospective study showing that patients with idiopathic VTE had a 60% higher risk of arterial events than those with secondary VTE [5]. *Bova et al.*, compared the incidence of subsequent arterial events in 151 consecutive patients with idiopathic VTE and a control group [6]. They concluded that arterial events were more common in patients with VTE. These results were not confirmed by other investigators, who hypothesize that conditions resulting from atherosclerosis may predispose people to VTE because of another associated morbidity, like hospitalizations or impaired mobility [7,8].

PATIENTS AND METHODS

We performed a case-control study to investigate the association between the classical cardiovascular risk factors (smoking, dyslipidemia, hypertension and diabetes mellitus) in 2 groups of patients, one with ischemic cerebrovascular disease (CVD) and another with venous thromboembolic disease (VTE). The study was approved by the Ethics Committee of our hospital.

We studied a group of 453 patients, 201 with VTE, and 252 patients with CVD (cases of cardioembolic stroke were excluded). The diagnosis of VTE was performed using Doppler ultrasound imaging. Pulmonary embolism (PE) was documented using ventilation/perfusion lung scan or computed tomography. Patients with a history of cancer were excluded. Stroke diagnosis was made based on acute onset and persistent neurological symptoms with a compatible cerebral image, once other causes had been ruled out. A control group consisting of 346 subjects with no history of arterial thrombotic disease, VTE or cancer was also included in the study.

All patients and controls were evaluated for the presence of the following risk factors: hypertension (diastolic blood pressure > 90 mmHg, on at least 2 occasions, or the use of hypotensive drugs); diabetes mellitus (fasting glucose level > 126 mg/dl, or the use of anti-diabetic drugs); dyslipidemia (fasting cholesterol level > 220 mg/dl, or high density lipoprotein (HDL) cholesterol level < 35 mg/dl, or total cholesterol/HDL cholesterol ratio > 4.5, or the use of lipid-lowering drugs); smoking (habitual daily intake of >10 cigarettes).

We conducted a descriptive study of the discrete variables (age and sex) and calculated the frequency and percentage of occurrence of each category (dyslipidemia, HTA, DM, and smoking status). For continuous variables, we calculated the descriptive statistics (mean, median, standard deviation, standard error, minimum, and maximum). The percentages were compared using Fisher's exact test. We calculated the p-value through univariate logistic regression models. All comparisons were made with a significance level of 0.05. The magnitude of the associations was estimated by odds ratio (OR) and confidence intervals at 95% (95%CI). In order to define properly the effect of the different variables, we conducted a multivariate logistic regression analysis adjusting for age and sex as well as those risk factors that could influence the outcome in each case. Statistical analysis of the data was performed using Stata v.10 (StataCorp LP, College Station, TX, USA).

RESULTS

The characteristics of the patients and the control group as well as the distribution of cardiovascular risk factors are shown in Table 1. Venous thrombotic events were divided into 5 groups depending on the location of the thrombus: PE (associated or not with DVT), 44.8% (n = 90); DVT in the lower limbs, 36.8% (n = 74); thrombosis of unusual locations, 11.9% (n = 24); superficial venous thrombosis, 4.5% (n = 9); and upper limb DVT, 2.0% (n = 4).

We analyzed separately the presence of cardiovascular risk factors and classical thrombotic risk in patients with venous thrombosis. In this group of patients, 64.1% had experienced spontaneous thrombotic events, not identifying any of the analyzed risk factors (immobilization, surgery, air travel, pregnancy, hormonal therapy or autoimmune disease). 26.6% of the patients had at least one risk factor, whereas in 9.3% of them, thrombosis was associated with the presence of 2 or more risk factors.

All the risk factors included in the present study (ie, hypertension, diabetes mellitus, dyslipidemia, and smoking) were associated with elevated risk of CVD. In patients with VTE, dyslipidemia and smoking were significantly more frequent than in the control subjects. Patients with alterations in the lipid profile had a higher risk of VTE (OR: 1.62, 95%CI: 1.04-2.52, p= 0.03), whereas subjects who smoke presented twice the risk of venous thrombosis (OR: 2.28, 95%CI:1.49-3.48, p=0.0001).

After adjusting for age and sex, when we compared the 2 patient groups and controls, the multivariable analysis showed that dyslipidemia was a risk factor for VTE (OR: 1.66, 95% CI: 1.06-2.61, p=0.027), and it was not related with CVD (OR: 1.29, 95% CI: 0.84-1.98, p: ns) (Table 1).

The distribution of the risk factors was further analyzed according to age, subgrouping subjects in ≤65 years and >65 years (Table 2). Hypertension was not related with an increased risk of VTE in patients older than 65 years (OR: 1.61; 95%CI: 0.83-3.12; p=0.1617) neither in younger patients (OR: 0.47; 95%CI: 0.23-0.95; p=0.0321); however, hypertension was a risk factor for CVD only in younger patients (OR: 3.00; 95%CI: 1.66-5.40; p=0.0002). Dyslipidemia was associated with significantly increased risk of

Table 1: Characteristics of the study population. OR values adjusted for age and sex.

		Patients (%) (VTE: 201; CVD:252)	Controls (%) (N=346)	OR	IC (95%)	p	CVD *vs* VTE
Age (±SD)	**CVD**	70.2±15.1	58.2±17.9	1.05	1.03-1.06	<0.0001	<0.0001
	VTE	50.6±18.7		0.98	0.97-0.99	0.0001	
Sex (women/men)	**CVD**	117/135	169/177	1.35	0.92-1.99	ns	0.4059
	VTE	102/88		0.77	0.53-1.11	ns	
Hypertension	**CVD**	144 (57.1)	113 (32.7)	1.56	1.05-2.29	0.025	<0.0001
	VTE	49 (24.5)		1.06	0.65-1.72	ns	
Diabetes	**CVD**	63 (25.0)	32 (9.2)	2.29	1.40-3.81	0.0009	<0.0001
	VTE	9 (4.5)		0.64	0.28-1.38	ns	
Smoking	**CVD**	65 (25.8)	61 (17.6)	3.08	1.92-5.02	<0.0001	0.0330
	VTE	71 (35.5)		2.31	1.51-3.54	0.0001	
Dyslipidemia	**CVD**	66 (26.2)	66 (19.1)	1.29	0.84-1.98	ns	0.5845
	VTE	47 (23.5)		1.66	1.06-2.61	0.027	

Table 2: Prevalence of risk factors according to age.

	≤ 65 Years			> 65 Years		
	CVD (OR, 95%CI, p) N= 80	VTE (OR,95%CI,p) N= 146	p	CVD (OR, 95%CI, p) N= 171	VTE (OR, 95%CI, p) N= 54	p
Hypertension	3.00; 1.66-5.40; 0.0002	0.47; 0.23-0.95;0.0321	<0.0001	1.48; 0.93-2.340.58-1.68; 0.0992	1.61; 0.83-3.12: 0.1617	0.8006
Diabetes	5.50; 2.32-13.05; <0.0001	0.62; 0.19-2.05; 0.4295	<0.0001	1.91; 1.09-3.340.58-1.68;0.022	0.51; 0.18-1.43; 0.1969	0.0056
Smoking	2.84; 1.65-4.89;0.0001	2.25; 1.43-3.56;0.0004	0.4073	2.18; 1.04-4.570.58-1.68;0.0355	2.64; 1.05-6.65;0.0337	0.6372
Dyslipidemia	2.59; 1.43-4.68; 0.0013	1.10; 0.63-1.93, 0.7333	0.0068	0.99; 0.58-1.68; 0.9643	2.13; 1.08-4.18;0.0266	0.0198

thrombosis in younger patients who developed VTE (OR: 2.13; 95%CI: 1.08-4.18; p=0.0266) or CVD (OR: 2.59; 95%CI: 1.53-4.68; p=0.0013), but not in older patients. Diabetes was a risk factor for CVD patients independently of age, but no association was found for development of a venous thrombotic event (table 2). Finally, smoking was a risk factor for all subgroups of patients independently of age and the type of thrombosis (Table 2).

DISCUSSION

Our study showed that arterial thrombosis and venous thrombosis share some cardiovascular risk factors. Our results for arterial thrombosis confirm that vascular risk factors play an important role in this entity, as previously described [9]. Regarding VTE, we have found some noteworthy associations. Smoking and dyslipidemia were a risk factor for both entities independently of age. Nevertheless, dyslipidemia was more prevalent in patients >65 years. On the other hand, hypertension was a risk factor for VTE only in patients ≤65 years.

Some studies show a relationship between atherosclerosis and venous thromboembolism, but the mechanism underling this association is not clear. Cardiovascular risk factors can contribute to the development of venous thrombus, activation of coagulation, to endothelial damage or stasis. Smoking increases fibrinogen levels and can activate the intrinsic pathway through endothelial damage or anoxia [10-14], whereas the diabetes mellitus is associated with decreased fibrinolysis and may contribute to venous stasis [15,16]. Moreover, hypertension is associated with some degree of inflammation and endothelial damage [17]. Diabetes and lipids are associated with a hypercoagulable state and reduced fibrinolytic activity.

Our results agree with those from a case-control study in a Japanese population reporting an association between elevated cholesterol levels and the occurrence of VTE [18,19]. The patients in the Japanese study did not present severe cardiovascular atherosclerotic disease, and therefore the author hypothesized that hypercholesterolemia directly affects the vein wall or causes progressive hemostatic derangement with impaired fibrinolysis. Even though the atherosclerotic process does not take place in the venous system, there seems to be an association between dyslipidemia and the risk of thrombosis [20]. The results obtained by *Deguchi et al.* in a group of men under 55 years indicated a relationship between alterations in the lipid profile and thrombosis [21]. In addition, results published by *Doggen et al.* showed decreased thrombotic risk in patients with elevated HDL levels (> 66.1 mg/dl) [22].

Smoking is a well-established risk factor for arterial disease, and one study has confirmed the role of smoking in venous thromboembolism. The "Nurses' Health Study" found smoking to be an independent risk factor for PE, with a relative risk of 1.9; this risk level increases with higher levels of cigarette intake [23].

Hypertension is well-established such a risk factor for cardiovascular disease, but its role in relation to VTE is controversial. This study has determined the presence of hypertension in 24.5% (n = 49) of patients with VTE, but not statistically significant association was found. Becattini et al. [24] found an OR of 1.9 for hypertension in patients with pulmonary embolism, while in another study of 215 patients showed an association between hypertension and thrombosis, with an odds ratio of 1.2 [25]. However, other publications have not been able to establish relationship with hypertension [1]. For example, in The Copenhagen City Heart Study, no association with elevated systolic pressure was found [26].

Diabetes mellitus is defined as a condition in which the levels of several factors involved in the processes of coagulation and fibrinolysis are altered [15]. The damage, dysfunction and failure of diverse organs that occurs in the long term could lead to other complications associated with an increased risk of VTE [16]. In the series of patients studied was not found association of DM with VTE. The prevalence of DM in the study population was 4.5 % (n = 9). These results confirm previously published that an independent relationship between the two entities are not evidence [16,26,27]. However, other there are studies in which the DM is associated with an increased risk of thrombotic event. In a meta- analysis published in 2008 established an OR of 1.42 for DM [1], while the LITE study reported a hazard ratio (HR) 1.7 [25]. On the other hand, results in a group of 302 patients indicate a thrombotic risk twice as high in individuals with DM [28].

The ARIC study and the Cardiovascular Health Study found that VTE incidence was not associated with smoking, hypertension, or lipid levels [25,29]. Diabetes has been associated with significantly increased risk of VTE, with a 1.7-fold risk (95%CI: 1.2-2.4). Furthermore, in patients with idiopathic first thrombotic event treated with low-dose aspirin following antigoagulant therapy, a reduction is seen in the ratio of major vascular events (myocardial infarction, stroke, or death from cardiovascular accident) [30]. Statins reduce the extrinsic system tissue factor pathway inhibitor, and patients undergoing statin therapy had significantly lower mean levels of D-dimer than those

who were not receiving the therapy [31]. Statins have several effects beyond cholesterol lowering, including inhibition of platelet aggregation, oxidation reduction, and anti-inflammatory activity. Some studies support the notion that venous thrombosis is less common in patients being treated with statins than in patients not receiving lipid-lowering therapy [32-34], although this difference may be due to their hypolipidemic effect owing to direct or associated inflammatory pleiotropic effects.

CONCLUSIONS

Our results show that arterial and venous thrombosis share common risk factors such as dyslipidemia, HTA, and smoking. Further studies are needed to clarify a possible association between arterial thrombotic and venous thrombotic disease, and to evaluate its implications for clinical practice.

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