V. Petrauskiene · M. Falk · I. Waernbaum ·
M. Norberg · J. W. Eriksson

The risk of venous thromboembolism is markedly elevated in patients with diabetes

Received: 6 August 2004 / Accepted: 25 November 2004 / Published online: 19 March 2005
© Springer-Verlag 2005

Abstract *Aims/hypothesis:* Diabetes mellitus is associated with several changes in coagulation and fibrinolysis that may lead to a thrombogenic propensity. However, it is not known whether these perturbations actually cause increased risk of venous thromboembolism. *Methods:* In a retrospective population-based study we evaluated the medical records of all 302 adult patients who were admitted to the Umeå University Hospital with verified deep vein thrombosis or pulmonary embolism during the years 1997 to 1999. The patients were classified as diabetic ($n=56$) and non-diabetic ($n=246$) according to clinical information. The total number of diagnosed diabetic patients in different age groups in the catchment area was obtained from computerised registries in the primary health care centres and the Umeå University Hospital, and data on the background population were collected from the Swedish population registry. *Results:* The annual incidence rate of venous thromboembolism among diabetic patients in the population was 432 per 100,000 individuals (95% CI 375–496). In non-diabetic individuals it was 78 (95% CI 68–88). The age-adjusted incidence rate among the diabetic population was 274 (95% CI 262–286). The annual incidence rate of venous thromboembolism was elevated in type 1 and type 2 diabetic patients and the incidence rates were 704 (95% CI 314–1,566) and 412 (95% CI 312–544) respectively. The overall standardised morbidity ratio was 2.27 (95% CI 1.75–2.95), i.e. diabetic patients were more prone to venous thromboembolism after adjustment for age differences. *Conclusions/interpretation:* These results suggest that the age-adjusted risk for venous thromboembolism is more than two-fold higher among diabetic patients than in the non-diabetic background population.

Keywords Deep vein thrombosis · Diabetes mellitus · Incidence rate · Pulmonary embolism · Venous thromboembolism

Abbreviations DVT: Deep vein thrombosis · IR: Incidence rate · PE: Pulmonary embolism · SMR: Standardised morbidity ratio · VTE: Venous thromboembolism

Introduction

There is increasing evidence that diabetes mellitus is associated with several defects of coagulation and fibrinolysis that lead to a procoagulant, thrombogenic predisposition [1]. Raised concentrations of fibrinogen, von Willebrand factor and other endothelium-derived mediators increase blood viscosity and promote platelet activation and adhesion. In addition, fibrinolysis is impaired by raised concentrations of plasminogen activator inhibitor-1. It is not known whether there is a generalised increased thrombotic tendency or whether the adverse haemostatic impact of diabetes is confined to the arterial tree, where it can contribute to the well-known increase in cardiovascular events [1–4]. If there is a generalised tendency for thrombus formation in the vasculature, diabetes would be expected to lead to an increased risk of venous thromboembolism (VTE), too. However, despite the great scientific interest in diabetic vascular complications, little is known about the risk of VTE in diabetic patients and data about this remain controversial. A few studies have suggested that diabetes is a significant risk factor for VTE [5, 6], but some studies suggest that diabetes does not increase the risk of thromboembolic events [1, 7, 8].

In the present retrospective study, we address the incidence of venous thromboembolism, i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE), in the Umeå University Hospital catchment area during 3 years, 1997–1999, and we show that the risk of VTE among diabetic patients is greater than in the non-diabetic population.

V. Petrauskiene · M. Falk · I. Waernbaum ·
M. Norberg · J. W. Eriksson (✉)
Department of Public Health and Clinical Medicine,
Umeå University Hospital,
901 85 Umeå, Sweden
e-mail: jan.eriksson@medicin.umu.se
Tel.: +46-90-7851853
Fax: +46-90-137633

Subjects and methods

Subjects We analysed the medical records of patients who had episodes of VTE during the years 1997 to 1999 and were admitted to the Departments of Medicine or Cardiology at the Umeå University Hospital. All adult patients in the catchment area (population ≥ 15 years=110,100) with diagnosis codes I80, I82 and I26 according to ICD, but excepting isolated superficial thrombophlebitis, were included. All VTE patients were hospitalised at the University Hospital during this time period. Subjects with post-surgery (<4 weeks) VTE and patients not resident in the catchment area were excluded.

Data about age, sex, VTE diagnosis, diagnostic methods, diabetes (type and treatment regime) were collected from medical records. We also obtained information about concomitant conditions such as coronary heart disease, atrial fibrillation or flutter, hypertension, congestive heart failure, cancer and immobilisation. To analyse data, all VTE cases were divided into two groups: diabetic and non-diabetic. Subjects were considered to have prevalent diabetes when this was documented in medical records or if they were receiving insulin or oral hypoglycaemic agents. No case of previously undiagnosed diabetes was found during the hospitalisation period. Of the 302 VTE patients, 56 had diabetes. According to the medical records, six of these had type 1 and 50 had type 2 diabetes. All type 1 and 18 type 2 diabetic patients were being treated with insulin, either alone or in combination with oral medication. Fourteen type 2 diabetic patients were being treated with oral hypoglycaemic agents, and 18 had non-pharmacological treatment. There were 246 non-diabetic VTE patients, and the sex distribution was even (Table 1). There were eight patients who had two thromboembolic episodes during the investigated period. They were included as one case each, and data from the first event were used for analyses. The study was approved by the Ethics Committee of Umeå University.

Diagnosis of DVT and PE DVT ($n=219$) was diagnosed by Doppler ultrasonography (182 patients/83.1%), phlebography (21/9.6%), or both of these methods (7/3.2%). For

seven patients (3.2%) DVT diagnosis was only clinical. Urography was used to diagnose renal vein thrombosis and computerised tomography for cava inferior thrombosis (one patient/0.5% for each).

PE ($n=83$) was diagnosed using angiography (41 patients/49.4%), ventilation/perfusion scintigraphy together with chest X-ray (14/16.9%), autopsy (11/13.3%) or a combination of these methods (6/7.2%). In several cases, PE was diagnosed using other methods such as clinical presentation only (8/9.6%), computerised tomography (1/1.2%), plasma-D-dimers (1/1.2%), cardiac ultrasound and arterial blood gas (1/1.2%).

Evaluation of incidence To evaluate the incidence of VTE, we obtained information from the Swedish population registry on the total number of inhabitants divided by age groups and sex in the catchment area (at the end of 1998). Data on the number of adult (≥ 15 years) patients diagnosed with diabetes were collected from computerised patient registries in the primary health care centres and the Departments of Medicine and Cardiology at Umeå University Hospital, giving an ascertainment greater than 95%, as virtually all adult diabetic patients in the area attend these units. In 1998, 284 type 1 and 4,041 type 2 diabetes patients were identified. This gives a prevalence of 0.26 and 3.67%, respectively among adults, which is consistent with previous results from northern Sweden [9]. Screening studies report somewhat higher numbers as they include asymptomatic subjects [10].

Statistical analysis The Student's paired *t*-test and chi square test were used for comparisons between the diabetic and non-diabetic groups, and a *p* value of less than 0.05 was considered significant. Incidence was calculated as incidence rate (IR) (cases per 100,000 adult inhabitants/year) and given with 95% CIs. In addition, for the diabetic population, IRs were also age-adjusted according to the age distribution of the non-diabetic population. The standardised morbidity ratio (SMR) was calculated to address age-adjusted risk associated with diabetes.

Table 1 Clinical characteristics of diabetic and non-diabetic patients with venous thromboembolism (VTE)

	Diabetic ($n=56$)	Non-diabetic ($n=246$)	<i>p</i> values
Age	71.1 $\pm$ 12.9	65.8 $\pm$ 16.7	$p=0.010$
Sex			
Men	31 (55.5%)	120 (48.8%)	NS
Women	25 (44.6%)	126 (51.2%)	NS
Type of VTE			
Deep vein thrombosis	34 (60.7%)	185 (75.2%)	$p=0.032$
Pulmonary embolism	22 (39.3%)	61 (24.8%)	$p=0.018$
Hypertension	19 (33.9%)	46 (18.7%)	$p=0.016$
Cerebrovascular diseases	10 (17.9%)	18 (7.3%)	NS
Coronary heart disease	16 (28.6%)	34 (13.8%)	$p=0.008$
Congestive heart failure	9 (16.1%)	17 (6.9%)	$p=0.036$
Arrhythmia (atrial fibrillation or flutter)	9 (16.1%)	28 (11.4%)	NS
Cancer	3 (5.4%)	32 (13%)	NS
Immobility	1 (1.8%)	13 (5.3%)	NS

Data are means $\pm$ SD or *n* (%)

Results

In total 302 patients (151 men, 151 women) were diagnosed with VTE during the investigated period and the annual IR was 91/100,000 (95% CI 81–102). The youngest patient was 19 and the oldest 95 years. The frequency of thromboembolic events increased with age in both groups (Fig. 1). Diabetic VTE patients were significantly older than non-diabetic, as shown in Table 1. There was also a difference in age between type 1 and type 2 diabetic patients (59.3 ± 11.6 and 72.5 ± 12.4 respectively, means $\pm$ SD, $p=0.038$). There were 219 documented cases with DVT (without concomitant PE), i.e. 72.5% of all VTE cases. Most patients experienced episodes of DVT involving lower extremities (210 cases), while seven patients had DVT in upper extremities, one had kidney vein thrombosis and one had thrombosis of v. cava inf. Episodes of PE were diagnosed in 83 patients (27.5%). Of those, seven patients had a combined DVT and PE diagnosis.

Data on crude and age-adjusted IRs, SMR and population risk attributed to diabetes are presented in Table 2. The annual IR of VTE was clearly higher in the diabetic population, and this also applied after age adjustment. The annual IR was significantly higher in type 1 (704; 95% CI 314–1,566) and type 2 diabetic patients (412; 95% CI 312–

544) than in the non-diabetic population. The higher IR in diabetes appears to apply across different age groups as shown in Fig. 1. IR in diabetic and non-diabetic patients was also calculated separately for men and women in different age groups but there were no consistent sex differences (data not shown).

Among non-diabetic VTE patients an isolated DVT diagnosis was more common than in diabetic VTE patients (75.2 and 60.7%, respectively, $p=0.03$), but the annual age-adjusted IR for DVT was still higher in diabetic than in non-diabetic subjects, 194 (95% CI 190–198) and 58 (95% CI 50–67) respectively, and the age-adjusted SMR for diabetic subjects was 1.9 (95% CI 1.2–3.0). Accordingly, diabetic VTE patients had PE significantly more often than non-diabetic VTE patients (39.3 and 24.8%, respectively, $p=0.018$) and the age-adjusted IR for PE was much higher in diabetic patients than in the non-diabetic population, 80 (95% CI 77–83) and 19 (95% CI 15–25), respectively with an SMR of 19.9 (95% CI 13.1–30.3).

The presence of other clinical conditions that might contribute to the risk for VTE is shown in Table 1. Diabetic patients had coronary heart disease, hypertension and congestive heart failure significantly more often than non-diabetic individuals. Of the women, six used oral contra-

Fig. 1 Annual incidence rates for venous thromboembolism in the diabetic (filled bars) and non-diabetic (open bars) populations in different age groups. CIs of 95% are indicated *within* or *above* each bar. * $p<0.05$

Table 2 Incidence rates of venous thromboembolism (VTE) and risk measures for the diabetic versus non-diabetic population

IR, overall	91 (81–102)
IR in non-diabetic subjects	78 (68–88)
IR in diabetic subjects	432 (375–496)
Age-adjusted IR in diabetic subjects	274 (262–286)
PAR	9.5 (0.5–18.5)
SMR	2.27 (1.75–2.95)

Incidence rate (*IR*) and population-attributable risk due to diabetes (*PAR*) are presented as cases per 100,000/year. Standardised morbidity ratio (*SMR*) represents the age-adjusted ratio for diabetic versus non-diabetic subjects. All data are given with 95% CIs

ceptive pills, one of whom had type 2 diabetes. Two non-diabetic women developed DVT during pregnancy.

During hospitalisation for VTE, 25 patients (8.3%) died. In the group of patients admitted to the hospital for DVT three patients died, all three non-diabetic. In contrast, the mortality of diabetic patients versus non-diabetic was higher in the event of PE, though the difference was not statistically significant (nine patients/40.9% and 13/21.3%, respectively). This could be partly explained by the higher age among diabetic patients. There was no significant difference in post-hospitalisation mortality in diabetic versus non-diabetic patients during follow-up until June 2002.

Discussion

In this pilot study we show that diabetes is a possible risk factor for VTE, as the age-adjusted incidence of DVT and PE was significantly higher in the diabetic than in the non-diabetic population. The increased VTE risk in diabetes patients could be due to the diabetic state itself, or to other risk factors that are associated with diabetes. Possibly, both explanations are true.

There are several well-established risk factors for VTE, including immobilisation, surgery, cancer and age [11, 12]. The risk of VTE is dramatically increased in the later decades of life [12] and we also found that the incidence of VTE, in particular DVT, increased with age. In this study, diabetic patients with VTE were significantly older than non-diabetic patients and that may suggest that the higher risk in diabetic subjects is mainly due to older age. However, by using SMR to adjust for age differences, we demonstrated that there is an age-independent, more than 2-fold risk elevation among diabetic patients, and this was also substantiated by incidence numbers in separate five-year age groups and by the age-adjusted IRs.

It is recognised that cancer is one of the major risk factors for VTE [13], but we did not find any clear difference in the prevalence of diagnosed cancer between diabetic and non-diabetic VTE patients. Venous stasis associated with prolonged immobilisation is also an important risk factor for VTE [14], but there was no significant difference in the frequency of documented immobilisation between diabetic and non-diabetic patients suffering VTE. Congestive heart failure is an independent risk factor for VTE, and this is

related to the degree of impairment of left ventricular ejection fraction [15]. In our study, the proportion of subjects with congestive heart failure was greater among the diabetic patients, probably partly as a consequence of hypertension and CHD. Cardiac failure leads to venous stasis and this, in combination with abnormalities in haemostasis and in platelet and endothelial function, should predispose diabetic subjects to development of venous thrombosis [16]. Moreover, obesity which is common in type 2 diabetes, could be an important factor and smoking might also be involved, but complete data were not available in this investigation.

The fact that diabetes leads to a greater increase in risk of PE than in risk of DVT suggests that diabetes not only has an impact on the development of venous thrombi, but also on the progression to a more severe condition with the detachment of emboli ending up in the pulmonary arteries. Diabetes, in particular type 2, is believed to affect fibrinolysis more severely than coagulation, and that could possibly have a greater impact on the occurrence of symptomatic PE vs DVT. Although type 2 diabetes in particular is considered to be strongly linked to dysregulated haemostasis, our present data suggest that type 1 diabetes is an equally strong risk factor for VTE. Hence the diabetic state itself appears to be important, but this should be examined in detail in larger studies.

There is very limited information in the previous literature about the associations between diabetes and VTE. The Framingham Study found no relationship between glucose levels and the occurrence of VTE [2]. In contrast, a longitudinal study that investigated associations between cardiovascular risk factors and incidence of VTE showed that diabetes and obesity were each associated with significantly increased risk of VTE independently of age, race and sex. Those with diabetes at baseline had a 1.7-fold greater risk (95% CI 1.2–2.4) than those with normal fasting glucose levels [12]. In the transplantation literature diabetes has been reported to be an important risk factor for VTE [6, 16]. In a retrospective study on patients undergoing kidney transplantation multivariate analysis identified diabetes as a significant risk factor for DVT (OR 2.0) and for PE (OR 2.6) [6], results which are compatible with our present findings in the general population. In addition, Bergqvist et al. in a prospective study on VTE following kidney transplantation identified diabetes as the most important risk factor [17].

We recognise that there are limitations in the present study that might have influenced the results. Methods verifying events of VTE vary between physicians, and both false positive and false negative results occur. Our case-finding may not be quite complete and, in addition, many VTE episodes are subclinical. Taken together, these circumstances might lead to under- or overestimation of the true number of cases in both the diabetic and non-diabetic cohorts. On the other hand, our overall IR is similar to other results [18]. Another problem in the study is that the number of diabetic patients in the total population as well as among VTE subjects may be underestimated because only those clinically diagnosed as having diabetes were considered as diabetic subjects. However, none of the above considerations is expected to markedly alter the finding of a higher

incidence of VTE among the diabetic patients. In the future, hopefully, a large prospective population-based study including a detailed characterisation of glucose tolerance will help to further clarify the relationship between diabetes and VTE, as well as the specific roles of factors such as hyperglycaemia, insulin resistance, type of diabetes and comorbidities.

In conclusion, we found that the age-adjusted risk of venous thromboembolism among diabetic patients is about two-fold higher than in non-diabetic subjects. The underlying mechanisms are not quite clear and it is not known whether the risk is explained mainly by diabetes itself or by concomitant conditions.

Acknowledgements Financial support was given by the Swedish Research Council (Medicine, 14287), the Swedish Diabetes Association and the Faculty of Medicine at Umeå University. We thank Hjordis Andersson and Pia Roslin for help with the evaluation of patient records.

References

1. Jones EW, Mitchell JRA (1983) Venous thrombosis in diabetes mellitus. *Diabetologia* 25:502–505
2. Kannel WB, McGee DL (1979) Diabetes and glucose tolerance as risk factors for cardiovascular diseases: the Framingham study. *Diabetes Care* 2:120–126
3. Howard VB (1996) Risk factors for cardiovascular disease in individuals with diabetes. *Acta Diabetol* 33:180–184
4. Norhammar A, Tenerz A, Nilsson G et al (2002) Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 359:2140–2144
5. Bergqvist D, Arnadottir M, Bergentz SE et al (1985) Juvenile diabetes mellitus—a risk factor for postoperative venous thromboembolism? *Acta Med Scand* 217:307–308
6. Humar A, Johnson EM, Gillingham KJ et al (1998) Venous thromboembolic complications after kidney and kidney–pancreas transplantation. *Transplantation* 65:229–234
7. Asplund K, Hagg E, Helmers C, Lithner F, Strand T, Wester PO (1980) The natural history of stroke in diabetic patients. *Acta Med Scand* 207:417–424
8. Partamian JO, Bradley RF (1965) Acute myocardial infarction in 258 cases of diabetes: immediate mortality and five year survival. *N Engl J Med* 273:455–461
9. Forrest RD (1990) Diabetes mellitus in North Sweden: prevalence assessed from prescriptions for anti-diabetic agents. *J Intern Med* 228:267–273
10. Eliasson M, Lindahl B, Lundberg V, Stegmayr B (2002) No increase in the prevalence of known diabetes between 1986 and 1999 in subjects 25–64 years of age in northern Sweden. *Diabet Med* 19:874–880
11. Drouet L (2001) Venous thromboembolic pathology: new acquired risk factors or new data on acquired risk factors. *Arch Mal Coeur Vaiss* 94:1318–1326
12. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR (2002) Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 162:1182–1189
13. Prandoni P, Lensing AWA, Bullen HR et al (1992) Deep vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 327:1128–1133
14. Kirkegaard A, Norgren L, Olsson CG et al (1987) Incidence of deep vein thrombosis in bedridden non surgical patients. *Acta Med Scand* 222:409–414
15. Howell MD, Geraci JM, Knowlton AA (2001) Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol* 54:810–816
16. Lip GY, Gibbs CR (1999) Does heart failure confer hypercoagulable state? Virchows triad revisited. *J Am Coll Cardiol* 33:1424–1426
17. Bergqvist D, Bergentz SE, Bornmyr S, Husberg B, Konrad P, Ljungner H (1985) Deep vein thrombosis after renal transplantation: a prospective analysis of frequency and risk factors. *Eur Surg Res* 17:69–74
18. Silverstein MD, Heit JA, Mohr DN et al (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 158:585–593