Physical activity, immobilization and the risk of venous thrombosis

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Chapter 6

Minor injuries as a risk factor for venous thrombosis

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Abstract

Background: Injuries increase the risk of venous thrombosis. So far, most research has focused on major injuries that are accompanied by other risk factors for VT, such as plaster casts and surgery. We studied the association of venous thrombosis with common minor injuries such as minor sural muscle ruptures and ankle sprains.

Methods: We performed a large population-based case-control study (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] study) including consecutive patients with a first deep venous thrombosis of the leg or pulmonary embolism and control subjects. Participants with malignant neoplasms, those who underwent surgery and those who had a plaster cast, or extended bed rest were excluded.

Results: Of 2471 patients 289 (11.7%) and of 3534 control subjects 154 (4.4%) had a minor injury in the 3 months preceding the venous thrombosis (patients) or completion of the questionnaire (controls). Venous thrombosis was associated with previous minor injury (odds ratio adjusted for sex and age (OR_{adj}) 3.1; 95% confidence interval (CI) 2.5-3.8) compared with those without any injury. The association was strongest for injuries that occurred in the 4 weeks before thrombosis and was not apparent before 10 weeks. Thrombosis was more strongly associated with minor injuries located in the leg (odds ratio adjusted for age and sex 5.1; 95% confidence interval 3.9-6.7), while those located in other body parts were not associated. A fifty-fold increased risk was found in factor V Leiden carriers with a leg injury compared with non-carriers without injury (OR 49.7 95%CI 6.8-362.7).

Conclusions: Minor injuries in the leg are associated with a greater risk of venous thrombosis. Because minor injuries are common, they could be major contributors to the occurrence of VT.

Introduction

Venous thrombosis is a multicausal disease affecting 1 to 3 per 1000 individuals each year [1;2]. Known risk factors are, among others, surgery, immobility, and several prothrombotic genetic variants [3]. So far, studies have focused on major injuries in hospitalised or deceased individuals and were found to be major risk factors for venous thrombosis [4-11]. However, apart from the injury itself, other risk factors for venous thrombosis will be present because of the major injury, such as surgery, plaster cast, hospitalisation and extended bed rest. The risk of so-called minor injuries that do not lead to these additional factors is unknown.

We set up a large population-based case-control study into the cause of venous thrombosis, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study). The present study had 4 main objectives; (1) to estimate the relative risk of venous thrombosis after a minor injury; (2) to investigate characteristics of minor injuries that contribute most to this risk such as location and type of injury; (3) to estimate the relative risk of venous thrombosis of common injuries; and (4) to identify high risk patients by assessing the joint effect of minor injuries with well known genetic predispositions.

Participants and Methods

Participants

From March 1, 1999, until August 31, 2004, all consecutive patients with a first venous thrombosis were recruited from six anticoagulation clinics in the Netherlands. These clinics monitor the anticoagulant treatment of all patients within a well-defined geographical area. All patients had a first episode of deep venous thrombosis in the leg (DVT) or a pulmonary embolism (PE) between the ages of 18 and 70 years. Of the 6331 eligible patients, 276 patients died before they were able to fill out a questionnaire, while 82 had a very short life expectancy and therefore did not participate in this study. Of the remaining eligible individuals 5051 (84.6%) participated.

Information regarding the diagnostic procedure was obtained via hospital records and family physicians for 4059 patients. A DVT was considered definite when a (Doppler) ultrasound showed the presence of a thrombus in the deep veins. A PE was considered definite when confirmed with a high probability VQ scan, positive spiral CT or angiogram.

A PE was considered probable when the diagnosis was based on a low or intermediate probability VQ scan, inconclusive spiral CT or angiogram. For some patients no information regarding the diagnostic procedure was available while other patients were registered at the anticoagulation clinic with a different or additional diagnosis than the one objectively confirmed. In those patients the diagnosis by which the patient was registered at the anticoagulation clinic was added. For these patients we considered a registered PE as probable and a registered DVT as definite. Only 4958 patients were included in whom the diagnosis was considered definite or probable.

Control subjects were included from 2 sources; (1) by inviting partners of patients (81.6% of the partners participated), and (2) by using a random digit dialing method (68.8% participated) [12]. All participants gave a written informed consent. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Data collection

In a standardised questionnaire participants reported injuries, surgeries, plaster casts and immobilizations covering the period 1 year prior to the index date, along with sport activities, standing height and weight and family history of venous thrombosis. Body mass index was calculated by dividing weight (kg) by height squared (m^2). The index date was defined as the date of diagnosis of the thrombotic event for the patients and the date of completing the questionnaire for the control subjects. The questionnaire was sent to all participants within a few weeks after registration at the anticoagulation clinic or after we contacted the individuals of the random digit dialling control group. During the first few months of the study, a pilot questionnaire was used which did not contain questions regarding injuries. These 156 patients and 41 control subjects were excluded.

Participants were asked to report the most recent injury prior to the index date in a separate specific question related to minor injuries. The questionnaire listed eight common injuries and included an open text field for other injuries. The injuries were categorized irrespective of patient or control status. Seventeen patients who reported an injury after their venous

thrombotic event were excluded. Only injuries that occurred in the three months before index date were included in the present analysis. Subjects who underwent surgery or had a plaster cast, a hospitalisation or extended bed rest at home for at least four days in the year before the index date were excluded (1631 patients, 1004 control subjects), as were individuals who had ever been diagnosed a having malignant neoplasms before the index date (580 patients, 233 control subjects). An additional 1396 partner controls were excluded because their corresponding patient was excluded for one of the reasons mentioned above.

DNA collection and laboratory analyse

Patients and their partners who were included between March 1, 1999 and May 31, 2002 and the random control group were invited to the anticoagulation clinic for a blood draw. Patients and their partners recruited from June 1, 2002 onwards and participants who were unable or unwilling to come to the anticoagulation clinic were sent buccal swabs to collect DNA. Factor V Leiden and the prothrombin 20210A mutation were measured simultaneously [13].

Statistical analysis

Odds ratios (ORs) were calculated as estimates of the relative risk of thrombosis with 95% confidence intervals (CIs). Odds ratios were adjusted for sex and age (OR_{adj}). Partners were matched to their patients to adjust for lifestyle factors resulting in 1260 eligible couples in a matched analysis, while all 2538 patients were contrasted to the random digit dialing controls (2331 subjects) in an unmatched analysis. For calculation of the overall risk we weighted the odds ratio of the matched analysis with the odds ratio obtained by the unmatched analysis. This included an adjustment for patients included in both matched and unmatched analysis. When analyzing the risk in men and women separately only random control subjects were used, as in most couples partners were of the opposite sexes.

The percentage of injuries per week was calculated by dividing the number of individuals with an injury during a particular week by the total number of individuals who did not have an injury prior to that date. We calculated the proportion of calf veins thrombosis and confidence intervals using the exact method. To assess the joint effect of injuries and the factor V Leiden and prothrombin 20210A mutations, ORs were calculated in the presence

of only one risk factor and in the presence of both risk factors, all relative to those individuals with neither risk factor. We also performed a case-only analysis, which results in a synergy index (SI). A SI of one or more indicates synergy on a multiplicative scale. All analyses were performed in SAS 9.1 (SAS institute Inc, Cary, North Carolina, USA).

Results

Overall 2471 patients and 3534 control subjects were included in the present analysis. Their characteristics are shown in table 1. Control subjects with injuries were slightly more often men (52.6% versus 46.6%) and younger (mean age 44.3 versus 46.9 years) compared with those without injuries (data not shown).

Table 1. Characteristics of study population.

	Patients	Control subjects
	N = 2471	N = 3534
Women, No. (%)	1314 (53.2)	1882 (53.3)
Age (5^{th} -95^{th} percentile)	47.8 (24.9-67.6)	46.2 (24.8-66.5)
BMI (5^{th} -95^{th} percentile) (kg/m^2)	27.0 (20.3-35.4)	25.4 (19.8-33.0)
Type of venous thrombosis		
PE, No. (%)	766 (30.9)	
DVT, No. (%)	1454 (59.1)	
DVT leg + PE, No. (%)	251 (10.0)	

Of the patients, 289 (11.7%) had a minor injury in the three months prior to the index date as did 154 control subjects (4.4%). Injury was associated with venous thrombosis (OR 3.0, 95%CI 2.4-3.6). Adjustment for sex and age did not change this risk estimate (OR_{adj} 3.1, 95%CI 2.5-3.8) nor did further adjustment for sport activities and body mass index (OR_{adj} 3.5, 95%CI 2.8-4.3). Injury in 67 patients and 57 control subjects who did not mention a specific date of the injury and was not associated with venous thrombosis (OR_{adj} 1.2, 95%CI 1.1-1.3). These individuals were excluded from all analyses. Random control subjects had slightly more often injuries (4.8 %) than partner controls (3.6%) in the three

months prior to the index date, resulting in slightly different estimated, the OR_{adj} if random controls was 2.8 (95%CI 2.3-3.6) and that of partner controls was 4.2 (95%CI 2.9-6.0).

Thrombosis was more strongly associated with injuries that occurred during the previous 4 weeks (OR_{adj} 4.0, 95%CI 2.8-5.9) than with less recent injuries (figure). Among the patients most injuries occurred in the two to three weeks before the venous thrombosis diagnosis, while fewer events happened in the week directly prior to the venous thrombosis.

In the three month time window, ORs for minor injuries were similar in men (OR_{adj} 3.0, 95%CI 2.1-4.1) and women (OR_{adj} 3.0, 95%CI 2.2-4.2) as were ORs for the young vs old; young, aged 18 to 39 years (OR_{adj} 3.3, 95%CI 2.3-4.6), middle aged 40 to 59 (OR_{adj} 3.1, 95%CI 2.3-4.2) and elderly, aged over 60 (OR_{adj} 3.3, 95%CI 1.5-7.4).

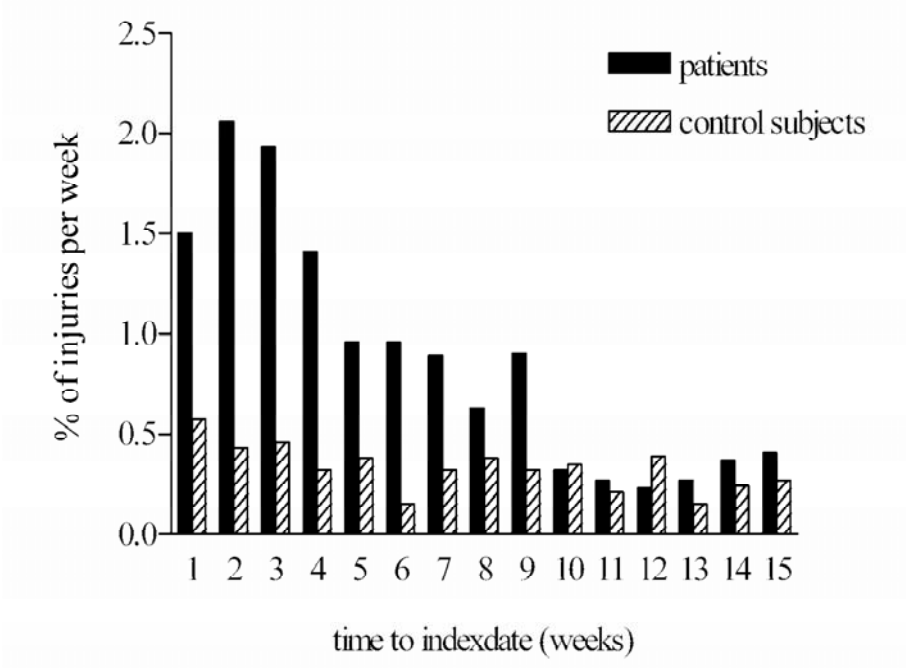

Figure. Percentage of injuries per week before the index date, which was the diagnosis of venous thrombosis (in patients) or completion of the questionnaire (in control subjects). The time window of the analysis concerned the first 13 weeks.

Location of injury

Of the 289 patients with a minor injury, 237 had their injury located in the leg (82.0%), compared with 78 out of 154 injuries among control subjects (50.6%). Therefore, thrombosis was more strongly associated with injury in the leg than with injury located in other body parts Individuals with an injury in the leg were therefore associated with a five-fold greater risk (overall OR_{adj} 1.1, 95%CI 0.8-1.6), table 2.

Table 2. Location of injury and the risk of venous thrombosis

Location injury	Patients	Control Subjects	Odd Ratio*
	2471	3434	(95%CI)
No Injury	2182	3380	1[#]
Leg	237	78	5.1 (3.9-6.7)
Arm	23	43	0.8 (0.5-1.4)
Trunk	14	24	0.9 (0.5-1.9)
Head	1	4	0.3 (0.0-2.4)
Unknown	14	5	3.0 (1.1-8.3)

*adjusted for sex and age - [#] reference group

Injuries in the leg were mainly associated with greater relative risk of an isolated DVT (OR_{adj} 6.3, 95%CI 4.7-8.5). The risk of an isolated PE (OR_{adj} 2.4, 95%CI 1.6-3.7) or a combination of PE and DVT (OR_{adj} 5.3, 95%CI 3.2-8.7) was also greater. For 1101 patients with a DVT, information was available regarding the location of the thrombus. Patients with a leg injury more often had a DVT in isolated calf veins (26.3%, 95%CI 18.9-33.6) compared with patients without an injury (14.5%, 95%CI 12.3-16.7).

Types of injury

(Partial) ruptures of muscles or ligaments in the leg were more strongly associated with a venous thrombosis than were other injuries such as sprains and contusions. Multiple injuries occurring simultaneously were strongly associated with venous thrombosis, table 3.

Table 3. Type of injury in the leg and risk of venous thrombosis

	Patients	Control subjects	Odds ratio*
	2419	3458	(95%CI)
No Injury	2182	3380	1[#]
Muscle or ligament Rupture	70	11	10.9 (5.6 - 21.3)
Contusion	6	5	2.0 (0.5 - 7.6)
Sprain	77	40	3.1 (2.1 - 4.6)
Multiple types of injury	24	4	9.9 (3.3 - 29.6)
Other	33	8	6.9 (3.1 - 15.0)
Unknown	27	10	4.6 (2.2 - 9.8)

*adjusted for sex and age - [#] reference group

Specific injuries most strongly associated with thrombosis were ruptures of the sural muscle ("tennis legs") and knee ligament ruptures while knee and ankle sprains were associated to a lesser extend with venous thrombosis, table 4.

Table 4. Specific injuries in the leg and their risk of venous thrombosis

Specific injuries	Patients	Control subjects	Odds ratio*
			(95%CI)
No Injury	2182	3380	1[#]
Rupture sural muscle (tennis legs)	56	5	22.5 (8.3 - 61.5)
Rupture knee ligaments	24	6	6.3 (2.6 - 15.0)
Ankle sprain	39	24	2.6 (1.6 - 4.1)
Knee Sprain or meniscus problems	47	16	5.1 (2.9 - 8.9)

*adjusted for sex and age - [#] reference group

Prothrombotic factors

In individuals who indicated having a first degree family member with a history of venous thrombosis, leg injury was associated with an estimated twelve-fold relative risk of venous thrombosis (OR_{adj} 12.0, 95%CI 5.9-24.7) compared with no injury in individuals without a family history. This finding suggests a joint effect with genetic factors. The estimated relative risk in carriers of the factor V Leiden mutation with an injury compared with noncarriers without an injury was almost 50 (table 5).

Table 5. Joint effect of prothrombotic mutations and injuries in the leg.

Prothrombotic mutations	Injuries	Patients 2243	Control subjects 2639	Odds ratio* (95%CI)
Factor V Leiden				
-	-	1623	2388	1[#]
+	-	351	135	5.0 (4.0 - 6.2)
-	+	181	59	6.8 (4.9 - 9.4)
+	+	39	1	49.7 (6.8 – 362.7)
FII 20210a mutation				
-	-	1874	2477	1[#]
+	-	100	46	3.4 (2.3 - 5.0)
-	+	206	55	7.0 (5.1 - 9.6)
+	+	14	2	8.6 (1.9 – 37.9)

*adjusted for sex and age - [#] reference group

Because the number of controls with an injury and the factor V Leiden mutation was low, a SI calculation in only patients was performed. This calculation (SI= (1623*39)/(351*181) = 1.0) suggested a joint effect at a multiplicative level and a thirty-fold (1.0*5.0*6.8=34) relative risk for those having the factor V Leiden mutation and a leg injury compared with those neither having the factor V Leiden mutation nor injuries.

The prothrombin 20210A mutation was associated with a 3-fold estimated relative risk of venous thrombosis among those without an injury (OR_{adj} 3.4, 95%CI 2.3-5.0). When both risk factors were present the estimated relative risk of venous thrombosis was nine-fold (OR_{adj} 8.6, 95%CI 1.9-37.9) compared with individuals without injury and the prothrombin 20210A mutation. The SI calculation (SI= (1874*14)/(206*100)= 1.3) suggested interaction at a multiplicative level and a thirty-fold (1.3*3.5*7.0=30) relative risk for the joint effect of the prothrombin 20210A mutation and leg injuries.

Discussion

Minor injuries that do not require surgery, a plaster cast or extended best rest were associated with a three-fold greater relative risk of venous thrombosis. The association appeared local as injuries in the leg were associated strongly with thrombosis, while injuries in other locations were not associated with venous thrombosis. The association was strongest for injuries that occurred in the month before the venous thrombosis, suggesting a transient effect. The association of venous thrombosis with leg injuries was strong in individuals with a genetic predisposition.

Most studies have focused on major or even fatal injuries. Because these studies were performed in hospitals, individuals who had an injury were also hospitalised and immobilised. Therefore it is difficult to make a distinction between the effect of hospitalisation, surgery, plaster cast, extended bed rest and the effect of injury. In studies that focused on major injuries, an asymptomatic venous thrombosis was detected in 0.4% to 12% of the trauma patients, despite prescribed prophylaxis [7-9;14]. One study found a three-fold increased risk of venous thrombosis after minor events[15]. However, minor events included among others travel, minor surgery and minor trauma and no information regarding minor trauma alone was available. Therefore, the risk of minor injuries could not be abstracted.

We found that the association of venous thrombosis with minor injuries was transient and that the excess risk disappeared after 10 weeks. Surprisingly, more injuries were found in the two to three weeks before the venous thrombosis compared with the week directly before the venous thrombosis. Although the differences were small and chance variation may have occurred, it is likely that this difference is true. It may take time before a clot becomes clinically apparent. However, this seems less probable as venous thromboses rates after air travel were highest in the first week after air travel [16]. More likely, because of the symptoms of the injury itself, the patient and physician may not recognise the venous thrombosis at first as the clinical characteristics are similar.

Injuries were strongly associated with venous thrombosis in individuals with genetic predisposition or a family history of venous thrombosis. We found a 50-fold greater risk in individuals with a factor V Leiden mutation and an injury. Because the risk associated with venous was highest in the first month after the injury and decreased sharply thereafter, we believe that many cases of venous thrombosis could be prevented when high-risk individuals with injuries would receive short-term prophylactic treatment. However, data are scarce and future research is needed to show whether this would be safe.

Several reasons why injuries increase the risk of venous thrombosis are conceivable. In 1856 Virchow described three main risk factors for thrombosis; hypercoagulability, stasis of the blood, and damage of the vessel wall[18]. First, several studies have shown an increased prothrombotic state in severely injured patients [19;20]. However, this increased prothrombotic state was not predictive of venous thrombosis in severely injured patients[20]. Because injuries not located in the leg were not associated with a higher risk of venous thrombosis in our study, we do not believe that a systemic reaction to minor injuries explains the thrombotic risk. Second, immobilisation leading to stasis of the blood could play an important role. To rule out this effect we excluded individuals with extended bed rest or immobilisation due to plaster casts. However, even minor injuries could have lead to reduced mobility, not necessarily bed rest, which could have led to thrombosis. Obstruction of the vein by oedema may have caused stasis as well. Third, damage of the vessel wall due to an injury may lead to a local increased risk of venous thrombosis.

Information on minor injuries was obtained after the thrombotic event. Patients could link their injuries to the thrombosis and therefore report the injury in the questionnaire, whereas control subjects do not have a specific event through which they can remember their injuries and therefore may not remember their injury (recall bias). However, the questionnaire for control subjects covered the period prior to filling it in. As risks were only increased up to 10 weeks, it seems likely that control subjects will have remembered their minor events during this period. A second reason why recall bias seems doubtful is that the risk of pulmonary embolism was also markedly increased and patients probably do not link their leg injury to pulmonary embolism. Referral bias could have occurred if physicians

would be more likely to diagnose or refer an injured patient for venous thrombosis examination. This would lead to an overestimation of the risk of venous thrombosis after injury. One study, also from the Netherlands, could not find a higher risk of being referred for venous thrombosis among women using oral contraceptives[21]. However, we do not know whether this is also true for minor injuries.

Our study showed that 4.4% of the control subjects had suffered a minor injury in the three months prior to indexdate. Since minor injuries are common, they can be responsible for many cases of venous thrombosis, as can be shown by the population attributable fraction. Of the patients 289 out of 2471 (11.7%) patients had a minor injury. The risk of venous thrombosis was three-fold increased, resulting in a population attributable fraction of 7.9% (11.7*(3.1-1)/3.1=7.9). Because other injuries were not associated with venous thrombosis risk, this population attributable fraction was entirely due to injuries in the leg (7.7%). This suggests that minor injuries in the leg may be involved in 8 percent of the venous thrombotic events.

The relative risk of venous thrombosis was estimated after minor injuries that did not require plaster cast, hospitalisation or extended best rest. As minor injuries are common they can be major contributors to the occurrence of venous thrombosis. Many individuals with minor injuries will have contacted the general practitioner first. Therefore, there may be an important task for general practitioners to identify subjects who are at a high risk of developing venous thrombosis, and subsequently to provide prophylactic measures.

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