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Relationship between proteinuria and venous thromboembolism

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Abstract Nephrotic syndrome is known to cause venous thromboembolism (VTE) due to urine loss of antithrombin III and activation of the coagulation system. We hypothesized that the degree of proteinuria may predict the development of VTE. This was a retrospective case-controlled study of in-patients urban academic teaching hospital from April, 2007 to March, 2009 and who had undergone an imaging study for VTE. All radiology reports (N = 1,647) for CT angiography of chest and Doppler sonogram of extremities were reviewed. The following data were collected: race/ethnicity, degree of proteinuria on urinalysis, serum protein and albumin levels, risk factors for VTE and renal function. The study population consisted of 284 patients with VTE and 280 age/sex matched controls. Relative to those who did not have proteinuria, patients who tested positive for protein had a 3.4-fold increased risk of VTE (odds ratio (OR) 3.4, 95% confidence interval [2.4, 5.0]). The association was unchanged when adjusted for other risk factors. Patients with proteinuria may have an increased risk of venous thromboembolism.

Keywords Venous thromboembolism · Proteinuria · Urinalysis

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Introduction

Hospitalized patients, when compared to the community at large, have an increase risk of venous thromboembolism (VTE) manifesting as pulmonary embolism (PE) and deep venous thrombosis (DVT) [1, 2]. For this reason, hospitalized patients are often given prophylactic unfractionated or low molecular weight heparin depending on underlying risk factors such as history of cancer, history of previous VTE, acute infection, acute respiratory disease, autoimmune disease, and congestive heart failure [2, 3]. Heparin prophylaxis in high risk patients has been shown to decrease the relative risk of developing VTE by 44–63% in several placebo controlled, randomized trials [4–6]. After clinical suspicion of VTE is raised, DVT is usually diagnosed with Doppler sonography of the extremity, while CT angiography is used to confirm PE. The disease is potentially fatal when complicated by pulmonary embolism [7].

It is well known that the nephrotic syndrome (edema, macroalbuminuria, hypoalbuminemia and hypercholesterolemia) increases the risk of developing VTE. This is based on several case studies and retrospective studies [8–11]. One retrospective study demonstrated that patients with nephrotic syndrome are more than twice as likely to develop DVT compared to the non-nephrotic population [11]. The underlying mechanisms that lead to a hypercoagulable state in patients with nephrotic syndrome are thought to be related to reduced antithrombotic factors including antithrombin III, protein C and S concentrations, impaired thrombolytic activity and increased activity of fibrinogen, and factors V and VIII [9]. A recent study in patients who had 24 h urinary albumin determinations, indicated that even microalbuminuria increased the risk of venous thromboembolism [12].

Although a 24 h urine collection is regarded as the gold standard for measuring proteinuria, the method is more elaborated, and is slower to be reported than the faster automated screening method of detecting proteinuria. However, little is known about the relationship between proteinuria found on urinalysis and the development of VTE.

To investigate the correlation between the degree of proteinuria and VTE we performed a retrospective case-controlled study.

Methods

Study design

A case-controlled study was performed in patients admitted to urban academic teaching hospital from April, 2007 to March, 2009. The population enrolled in this study were at least 18 years of age at the time of admission who had undergone imaging studies on suspicion of thromboembolism with CT angiography of the chest or Doppler sonogram of the lower extremities, and who had had an automated urinalysis within 24 h of hospitalization. Demographics such as age, ethnicity and gender were recorded, as were serum laboratory values such as serum protein, albumin and creatinine. In addition, details of the medical history and the type of pharmacological VTE prophylaxis were collected. Patients with a previous history of VTE were excluded since it was challenging to differentiate between acute and chronic VTE with imaging studies alone.

Patient with recent surgery (within 3 month of hospitalization), pregnancy, coagulation disorder, chronic kidney disease (defined as serum creatinine 2.0 mg/dl and over), nephrotic syndrome, and those receiving therapeutic heparin or coumadin before the onset of VTE were also excluded.

Radiology reports on a total of 1,647 CT angiograms of the chest and Doppler sonograms of extremities were reviewed. Of the collected data, 342 patients were excluded because of missing urinalysis. Of the remaining 1,305 patients, 310 patients were found to have VTE (217 with DVT and 93 with PE). The age and sex matched control group was randomly selected from a group of 995 patients who underwent the imaging studies and were negative for VTE. Of the 310 eligible case and control patients, 26 and 30 patients were excluded respectively because they possessed one or more of the exclusion criteria, leaving 284 patients with VTE and 280 patients without VTE.

Data collection

Medical records, laboratory data and pharmacy database were reviewed. The two investigators (SK and SC) who collected the clinical data were blinded for the VTE status of those enrolled. Proteinuria was reported as 0, trace, 1+, 2+, and 3+. Proteinuria was considered as negative if reported as 0 and trace. The positive proteinuria of 1+, 2+, and 3+ correlated with approximately 30, 100 and 300 mg/dl of protein respectively. Urinalysis was evaluated using an automated urine chemistry analyzer (Clinitek Atlas®, Siemens, Carousel). The study was approved by the Beth Israel Institutional Review Board.

Statistical analysis

Univariate and multivariate logistic regression analysis were performed to estimate the odds ratio and the associated 95% confidence intervals (CIs) associated with the degree of proteinuria. Results from the univariate and multivariate models were similar. Final multivariate models were created through stepwise elimination of variables of interest from univariate analysis. *P* values of less than 0.05 for associations were considered to indicate statistical significance. SAS/STAT software was used for all analysis.

Results

Two hundred and eighty four patients with a first venous thromboembolism and 280 control subjects who had an imaging study for venous thromboembolism were enrolled in the study.

In the univariate analysis, case and control patients were similar with regard to age, and sex, but case patients were more likely than control patients to be black and less likely to be of Asian ethnicity (Table 1). These two groups were not significantly different in term of past medical history of cancer, congestive heart failure, pulmonary disease such as asthma or chronic obstructive pulmonary disease (COPD), autoimmune disease such as rheumatoid arthritis, lupus erythematosus, scleroderma, and inflammatory bowel disease, cerebral vascular accident (CVA), hypertension, hyperlipidemia, and coronary artery disease, whereas control patients were more likely than case to have a history of diabetes mellitus. VTE prophylaxis with unfractionated heparin 5,000 units every 8 h given subcutaneously was associated with less VTE (OR 0.49, 95% CI [0.27, 0.91]) but prophylaxis with subcutaneous unfractionated heparin 5,000 units every 12 h or enoxaparin 40 mg daily did not significantly reduce the development of VTE (Table 1). Low serum albumin (3.4 g/dl and under) and low serum protein ($\leq$6.2 g/dl) were weakly associated with an increased risk of developing VTE (Table 2). Six patients with VTE and 14 patients from the control group had no measurements of serum protein and albumin. Subgroup analysis of VTE and degree of proteinuria among patients

Table 1 Baseline characteristics of study patients

	VTE (N = 284)	No VTE (N = 280)	*P* value
Demographic characteristics			
Female	162 (57)[a]	155 (55)	0.7
Male	122 (43)	125 (45)	0.7
Age	66 ± 17[b]	65 ± 17	1
Black	48 (17)	28 (10)	0.02
White	91 (32)	80 (29)	0.4
Hispanic	72 (25)	83 (30)	0.3
Asian	12 (4)	28 (10)	0.01
Other	61 (21)	60 (21)	0.9
Past medical history			
Malignancy	42 (15)	45 (16)	0.1
Congestive heart failure	21 (7)	30 (11)	0.2
Pulmonary disease[c]	52 (18)	58 (21)	0.5
Autoimmune disease[d]	6 (2)	8 (3)	0.6
Cerebral vascular accident	17 (6)	16 (6)	1
Diabetes mellitus	61 (21)	83 (30)	0.03
Hypertension	148 (52)	139 (50)	0.6
Dyslipidemia	49 (17)	54 (19)	0.6
Coronary artery disease	40 (14)	47 (17)	0.4
VTE prophylaxis			
Unfractionated heparin 5,000 units every 12 h	194 (68)	188 (67)	0.8
Unfractionated heparin 5,000 units every 8 h	17 (6)	32 (11)	0.02
Enoxaparin 40 mg daily	8 (3)	5 (2)	0.6

[a] Number (percent)

[b] Mean ± SD

[c] Defined as chronic obstructive pulmonary disease and asthma

[d] Defined as rheumatoid arthritis, lupus erythematosus, scleroderma, and inflammatory bowel disease

Table 2 Laboratory characteristics of study patients

	VTE (N = 284)	No VTE (N = 280)	*P* value
Serum creatinine 0.9 mg/dl and under	165 (58)	179 (64)	–
Serum creatinine 1-1.9 mg/dl	119 (42)	101 (36)	0.2
Serum albumin 3.5 g/dl and over	104 (37)[a]	122 (46)[b]	–
Serum albumin 3.4 g/dl and under	174 (63)[a]	144 (54)[b]	0.05
Serum protein 6.3 g/dl and over	135 (49)[a]	154 (58)[b]	–
Serum protein 6.2 g/dl and under	143 (51)[a]	112 (42)[b]	0.03
Poteinuria			
Negative	127 (45)	206 (74)	–
Positive	157 (55)	74 (26)	<0.01
Severity of proteinuria			
1+	75 (26)	50 (18)	<0.001*
2+	63 (22)	16 (6)	<0.001*
3+	19 (7)	8 (3)	<0.002*

* *P* value relative to negative proteinuria

[a] N = 278; 6 patients did not have this variable

[b] N = 266; 14 patients did not have this variable

with mildly elevated serum creatinine, diabetes, and hypertension indicate positive proteinuria remains to be significant factor for the development of VTE (Table 3).

The odds ratio for VTE increased significantly when urinalysis was positive for proteinuria (OR 3.44, 95% CI [2.42–4.90]). Moreover, 2+ proteinuria (OR 6.39, 95% CI [3.53–11.54]) and 3+ proteiunuria (OR 3.85, 95% CI [1.64–9.06]) showed stronger correlation with VTE compared to 1+ proteinuria (OR 2.43, 95% CI [1.60–3.71]) (Table 4; Fig. 1). These results were similar when adjusted for other possible confounding factors.

Discussion

This case-control study provides support for the association between venous thromboembolism and automated detection of proteinuria who were admitted to hospital for

Table 3 Subgroup analysis of VTE and the degree of proteinuria among patients with mildly elevated serum creatinine, diabetes and hypertension

Degree of proteinuria	VTE	No VTE	*P* value*
Patients with serum creatinine of 1–1.9 mg/dl (N = 220)			
1+	37 (17)[a]	16 (7)	<0.001
2+	30 (14)	8 (4)	<0.001
3+	16 (7)	5 (2)	<0.001
Negative	36 (16)	72 (33)	–
Patients with diabetes mellitus (N = 144)			
1+	15 (10)	9 (6)	0.001
2+	17 (12)	6 (4)	<0.001
3+	7 (5)	3 (2)	0.008
Negative	22 (15)	65 (45)	–
Patients with hypertension (N = 287)			
1+	44 (15)	25 (9)	<0.001
2+	36 (13)	8 (3)	<0.001
3+	10 (3)	6 (2)	0.05
Negative	58 (20)	100 (35)	–

* *P* value relative to negative proteinuria among each subgroup

[a] Number (percent)

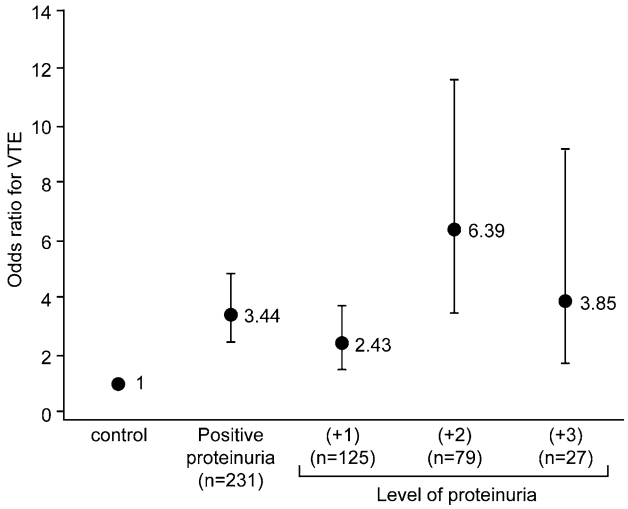

Fig. 1 Association of automated detection of proteinuria and VTE

medical illnesses. The higher degree of proteinuria was associated with a higher likelihood of VTE.

Several studies in the past have addressed the link between microalbuminuria or proteinuria and the risk of VTE [12, 13]. One study showed a two fold increased risk of VTE associated with microalbuminuria evaluated by 24 h urine collection in general non-hospitalized patients [12]. Another study demonstrated the association of dipstick positive proteinuria and reduced glomerular filtration rate and increased risk of VTE in patients with atrial fibrillation [13]. Microalbuminuria is also known to be an independent predictor of arterial thrombosis [14, 15]. The uniqueness of the present study would be that the simplest assessment of the degree of proteinuria could predict increased risk of VTE events.

Although a cause and effect relationship cannot be inferred from a case-control study, our findings have confirmed and extended past studies into the realm of identifying a simple predictive test for development of VTE. There are several mechanisms to explain the association between proteinuria, especially nephrotic range, and the risk of VTE: lower free protein S levels, reduced protein C activity and urinary loss of antithrombin [16–18], and activation of the coagulation system [19], as well as intravascular volume depletion. Moreover, microalbuminuria is considered to reflect systemic dysfunction of the vascular endothelium, haemostasis, and fibrinolysis especially in patients with hypertension and diabetes, this may be another mechanism that increases the risk of VTE [20, 21].

Our study has some potential limitations. All patients enrolled in the study had diagnostic imaging for suspected

Table 4 Results of logistic modeling

	Univariate			Multivariate[a]		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Positive proteinuria	3.44	[2.42, 4.90]	<0.001	3.21	[2.22, 4.63]	<0.001
1+ Proteinuria	2.43	[1.60, 3.71]	<0.001	2.20	[1.43, 3.40]	<0.001
2+ Proteinuria	6.39	[3.54, 11.5]	<0.001	6.45	[3.46, 12.0]	<0.001
3+ Proteinuria	3.85	[1.64, 9.06]	<0.002	3.61	[1.51, 8.62]	0.004
Black	1.83	[1.11, 3.01]	0.02	1.47	[0.86, 2.52]	0.16
Asian	0.4	[0.20, 0.80]	0.01	0.38	[0.18, 0.81]	0.01
Diabetes mellitus	0.64	[0.44, 0.95]	0.03	0.66	[0.44, 0.99]	0.04
Unfractionated heparin 5,000 units every 8 h	0.49	[0.27, 0.91]	0.02	0.52	[0.27, 0.99]	0.02
Serum albumin 3.4 g/dl and under	1.41	[1.01, 2.00]	0.05	1.3	[0.90, 1.88]	0.16

[a] Adjusted for significant confounding factors

VTE, which might reflect a higher awareness of risk by the admitting physician. Patients who had high clinical suspicion of VTE but did not have diagnostic imaging or asymptomatic VTE are not included in this study. We could not use pulmonary angiography, the current golden standard for diagnosis of PE, due to the retrospective nature of this study. However, CT angiography of the chest is becoming established as the first line imaging study in daily practice [22]. Due to its retrospective study design, other information for VTE risk factors such as immobility, length of hospital stay at the time of developing VTE, and infection during hospitalization is lacking. Also the factors that may cause transient microalbuminuria such as fever, dehydration and glycemic control during their hospitalization were not able to obtain. Because the result of urine dipstick test is crude estimate of urine protein concentration and depend on the amount of urine production, degree of proteinuria on urine dipstick test may be difficult to interpret. Higher values should be confirmed by repeated urine dipstick or obtaining urine protein to creatinine ratio.

The point estimate of the odds ratio of developing VTE decreased from 2+ (OR 6.4, 95% CI [3.5, 11.5]) to 3+ proteinuria (OR 3.9, 95% CI [1.6, 9.1]) but this can be due to lack of sufficient statistical power, as only 27 patients were positive for 3+ proteinuria, while an increasing risk of VTE from 1+ proteinuria to 2+ proteinuria was observed.

Further prospective study is necessary to compensate for these limitations.

In conclusion, automated detection of proteinuria was independently associated with development of in hospital VTE. Further large prospective study is warranted to investigate the correlation between proteinuria and VTE.

References

1. Heit JA, Melton LJ III, Lohse CM, Petterson TM, Silverstein MD, Mohr DN et al (2001) Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc 76:1102–1110
2. Francis CW (2007) Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. N Engl J Med 356:1438–1444
3. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR et al (2008) Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 133(6 Suppl):381S–453S
4. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W et al (2006) Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 332:325–329
5. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ (2004) Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 110:874–879
6. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C et al (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in medical patients with Enoxaparin Study Group. N Engl J Med 341:793–800
7. White RH (2003) The epidemiology of venous thromboembolism. Circulation 107(23 Suppl 1):I4–I8
8. Ambler B, Irvine S, Selvarajah V, Isles C (2008) Nephrotic syndrome presenting as deep vein thrombosis or pulmonary embolism. Emerg Med J 25:241–242
9. Singhal R, Brimble KS (2006) Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thromb Res 118:397–407
10. Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L et al (2008) High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. Circulation 117:224–230
11. Kayali F, Najjar R, Aswad F, Matta F, Stein PD (2008) Venous thromboembolism in patients hospitalized with nephrotic syndrome. Am J Med 121:226–230
12. Mahmoodi BK, Gansevoort RT, Veeger NJ, Matthews AG, Navis G, Hillege HL et al (2009) Microalbuminuria and risk of venous thromboembolism. JAMA 301:1790–1797
13. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L et al (2009) Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 119:1363–1369
14. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B et al (2001) Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 286:421–426
15. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H et al (2004) Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 110:32–35
16. Vigano-D'Angelo S, D'Angelo A, Kaufman CE Jr, Sholer C, Esmon CT, Comp PC (1987) Protein S deficiency occurs in the nephrotic syndrome. Ann Intern Med 107:42–47
17. Boneu B, Bouissou F, Abbal M, Sie P, Caranobe C, Barthe P (1981) Comparison of progressive antithrombin activity and the concentration of three thrombin inhibitors in nephrotic syndrome. Thromb Haemost 46:623–625
18. Kauffmann RH, Veltkamp JJ, Van Tilburg NH, Van Es LA (1978) Acquired antithrombin III deficiency and thrombosis in the nephrotic syndrome. Am J Med 65:607–613
19. de Sain-van der Velden MG, Kaysen GA, de Meer K, Stellaard F, Voorbij HA, Reijngoud DJ et al (1998) Proportionate increase of fibrinogen and albumin synthesis in nephrotic patients: measurements with stable isotopes. Kidney Int 53:181–188
20. Pedrinelli R, Giampietro O, Carmassi F, Melillo E, Dell'Omo G, Catapano G et al (1994) Microalbuminuria and endothelial dysfunction in essential hypertension. Lancet 344(8914):14–18
21. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ (1992) Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 340(8815):319–323
22. Schoepf UJ, Goldhaber SZ, Costello P (2004) Spiral computed tomography for acute pulmonary embolism. Circulation 109: 2160–2167