

Original Article

Diabetes mellitus-associated hyperglycemia is a risk factor for recurring deep vein thrombosis and post-thrombotic syndrome-a cohort study

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Abstract: Objective: Diabetes mellitus (DM) is one of the risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE). However, whether DM-associated hyperglycemia (HG) increases the incidence of recurrence in patients with a history of DVT is unknown. We performed a retrospective cohort study to identify the role of DM-associated HG in predicting DVT complications. Methods: One thousand two hundred and fourteen patients with a first-time diagnosis of DVT in the lower extremity received standard anti-thrombotic therapy in our hospital (from January 2000 through June 2009) and were followed up for at least 60 months. Excluded specific thrombotic comorbidities, 76 cases with DM were enrolled in the DM group, and 181 non-DM patients were added to the non-DM group. Recurrent events, post-thrombotic syndrome (PTS), treatment duration, re-patency of thrombosed lower extremity, and laboratory reports were compared between the groups. Multivariable logistic regression models were used to identify independent predictors of DM-associated HG. Results: Compared to the non-DM subgroup, DM patients with HG (60 patients) were significantly more likely to suffer from a high rate of recurrence ($P=0.021$) and PTS ($P<0.001$), an increased HR of recurrence (DM-associated HG among non-DM subgroup, $HR=1.34$, 95% CI: 1.09-1.63, $P=0.025$), prolonged treatment duration with anti-thrombotic therapy ($P=0.048$), decreased re-patency of lower thrombosed extremity ($P<0.001$), and exacerbation of the inflammatory reaction by a persistently high level of C-reactive protein (CRP) ($P=0.012$). Conclusion: These results suggest that, among DVT patients, DM with HG is associated with a poor prognosis, possibly due to thrombotic inflammation.

Keywords: Deep vein thrombosis (DVT), diabetes mellitus (DM), hyperglycemia (HG), post-thrombotic syndrome (PTS), thrombotic inflammation

Introduction

Diabetes mellitus (DM) is one of the risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Although some investigators have suggested that the risk of DVT is markedly increased in patients with diabetes [2], this risk is generally considered to be far less than that attributed to advanced age, long-term immobilization (cerebral palsy, paraplegia caused by spinal injury, economy class syndrome), major surgery (especially hip replacement), malignant diseases, hormone replacement therapy (HRT), major trauma (fractures), smoking, and a history of thrombosis. Moreover, other investigators have suggested that diabetes is not an independent risk factor for venous thromboembo-

lism (VTE) [3, 4]. However, in keeping with the Virchow's triad, hyperglycemia (HG) is associated with stasis [5, 6], endothelial injury resulting in damage to blood vessel walls [7-10] and hypercoagulation [11, 12], thereby increasing the risk of VTE. Clinically, some patients who receive standard anti-coagulation therapy still have a high risk of recurrence and post-thrombotic syndrome (PTS). PTS is a complication of DVT that can lead to chronic venous insufficiency (CVI) and ulceration. Some clinicians have suggested that thrombotic inflammation and damage to the venous endothelium are the main causes of PTS in DVT patients [13]. Previous studies have also suggested that HG increases the risk of thrombosis in critically ill patients and after major surgery [14]. The fact

DM associated HG is a risk for recur DVT & PTS

that DM amplifies the risk of thrombotic inflammation and venous endothelial injury suggests a correlation with the incidence of PTS [15, 16]. However, whether DM-associated HG is a predictor of outcome in DVT patients remains unclear, and the underlying mechanism supporting this association is unknown.

DM-associated HG has been shown to damage endothelial cells, induce endothelial dysfunction, up-regulate the expression of basement components, and increase procoagulant activity [7, 17-23]. In an in vivo study, Bouzeghrane et al. [17] showed that DM impairs DVT resolution through altered inflammatory, fibrinolytic, and matrix metalloproteinase (MMP) responses. In an in vitro study, we also found that persistently high glucose levels induce venous endothelial cell dysfunction and apoptosis through activation of the TNF/TNFR/TRAF-2 pathway [21]. HG causes inflammation and interrupts the balance between thrombosis and hemostasis, suggesting that there may be a more general association between DM and DVT prognosis.

We hypothesized that refractory HG in DVT patients with DM would be associated with a poor prognosis due to a persistent thrombotic inflammatory status. Indeed, in this cohort study, our results demonstrated that DM-associated HG was a poor prognostic factor in DVT patients due to a persistent thrombotic inflammatory effect. To investigate this further, we identified a subgroup of DVT patients with DM-associated HG and compared the rates of recurrent VTE and PTS, hazard ratios (HR), treatment duration and laboratory reports in these patients to the corresponding risk in patients with DM (normal blood glucose) or without DM. In addition, we sought to determine whether DM-associated HG should be considered a predictor of outcomes in DVT.

Methods

Cohort study design and setting

We conducted a retrospective, longitudinal cohort study at The Vascular Institute, First Affiliated Hospital of Sun Yat-sen University. An integrated system of electronic medical records, pharmacy data, and laboratory results along with the hospital database were used to identify patients, treatments, and outcomes. Approval to conduct this study was obtained

from the Institutional Review Board and Ethics Committees of First Affiliated Hospital, Sun Yat-sen University. All the participants provided their written informed consent to participate in this study.

Patients and data collection

The cohort in this observational study was composed of 1,214 patients who were older than 18 years of age and received a first-time diagnosis of DVT (venous thromboembolism of the lower extremity) in our hospital. These patients were referred between January 2000 and June 2009 and were followed (for at least 60 months, 60~120 months) in the outpatient department. Patients were excluded if they had a prior VTE or if they were lost to follow-up during the 60-month period.

Post-diagnostic treatments

All patients initially received therapeutic doses of low-molecular-weight heparin (LMWH) alone, followed by the combination of LMWH and warfarin. In high-risk situations, such as surgery, trauma, or immobilization, patients received thromboprophylaxis with LMWH according to the local standard practice based on national or international guidelines. Each patient who enrolled in the cohort study had symptoms associated with DVT, including swelling of the affected extremity, pain or tenderness, warmth, red or discolored skin, visible surface veins, leg fatigue, etc. Additional examinations were performed to gather objective evidence, including color duplex sonography, chest X-ray, electrocardiogram (ECG), and laboratory results (routine blood tests, tests for the presence of an acute infection, thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, and routine biochemical blood panels). Some patients with suspected PE received arterial blood gas analysis; measurement of fibrin degradation product (FDP), antithrombin III (ATIII), or factor VIII (FVIII); pulmonary perfusion/ventilation scanning; and possibly computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Patients who received warfarin therapy in excess of 90 days were subjected to a duplex ultrasound twice during the follow-up period. Patients who were discharged from the hospital were subjected to laboratory studies monthly while taking warfarin. These tests were then

DM associated HG is a risk for recur DVT & PTS

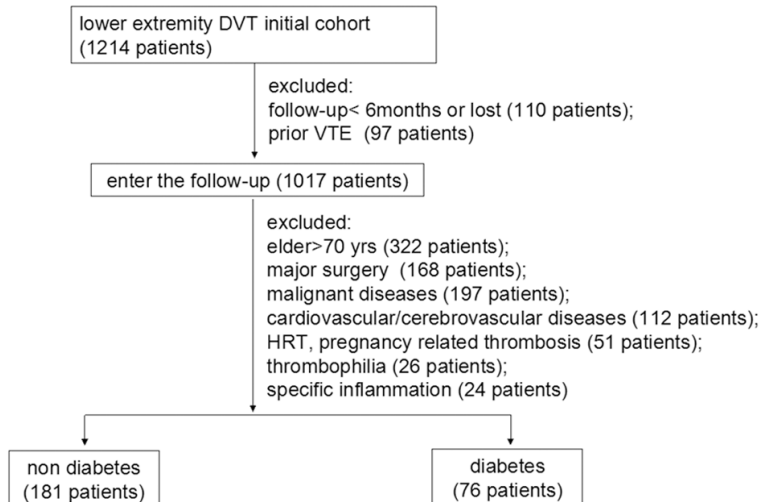


Figure 1. Study flow diagram. *Lost to follow-up, including patients who withdrew without a doctor's recommendation and those who were not re-checked with vein Doppler ultrasonic testing and blood testing (including thrombin time, prothrombin time, activated partial thromboplastin time, and fibrinogen) during treatment with warfarin. DVT: deep vein thrombosis. VTE: Venous thromboembolism.

stopped until the transference cure and warfarin treatment was discontinued. The process for defining the study cohort is described in **Figure 1**.

The first occurrence of anticoagulant-related complications (thromboembolism, bleeding, and death) was determined as previously described [24]. Briefly, specific complications requiring admission to the emergency department or hospital were identified using the ICD-9 discharge diagnosis codes from the hospital databases. All events were subsequently confirmed by 3 investigators who independently reviewed the patient's electronic and paper medical records.

DVT definition of complications and PTS scoring system

Thromboembolic complications were defined as PTS (pain, swelling and buildup of fluid, venous reflux, hyperpigmentation, skin ulcers, secondary varicose veins, recurring DVT or PE, etc.) and visceral venous thrombosis (mesenteric venous, renal vein or cerebral venous thrombosis, etc.). Recently, some clinicians have used the Villalta score [25] measured on days 30, 90 and 180. The use of the Villalta score for defining the presence and severity of PTS has been recommended by the ISTH

because it has been shown to be valid, reliable and sensitive to change over time [26]. In brief, patients are asked to rate five symptoms (pain, heaviness, cramps, paresthesia and pruritus) on a four-point scale from 0 (none) to 3 (severe). Six clinician-graded signs (edema, redness, hyperpigmentation, skin induration, venous ectasia and pain on calf compression) are evaluated using the same scale. The scores are then added, and PTS is considered to be present when the score is ≥ 5 . Classification of severity is performed as follows: 5-9 mild; 10-14 moderate; and >14 severe ulceration. In this study, a single investigator undertook all assessments, and a score ≥ 5 on two consec-

utive visits (day 90 and 180) indicated PTS. Bleeding complications included episodes of intracranial bleeding, gastrointestinal hemorrhage, hematoma, hemoptysis, epistaxis, and hematuria. All bleeding episodes that resulted in an admission to the emergency department or hospital were included regardless of severity. Fatal events were assessed for the presence of a direct relationship to bleeding or thromboembolism using the medical record and death certificate. Treatment duration was mainly a function of the international normalized ratio (INR) (a value of 2~3), syndrome relief or re-patency in the thrombosed vessel after treatment.

DM-associated HG population definition and classification

We define non-DM with HG patients as fasting blood glucose >7.0 mmol/L at the early period of DVT, but the OGTT test is normal and the diagnostic 2 h PG value below 11.1 mmol/L. We diagnosed patients with DM based on the established criteria for diabetes. HG was defined as a fasting blood glucose >7.0 mmol/L, detected at 7:00 am in the morning before breakfast. DM-associated HG was defined as patients who were previously diagnosed with DM and failed to maintain their fasting blood glucose below 7.0 mmol/L with hypoglycemic

DM associated HG is a risk for recur DVT & PTS

Table 1. Characteristics of the patients entering the follow-up period and completing the cohort study

Variable	DM	Non-DM
Male gender	82 (63.56%)	557 (62.73%)
Affected left extremity	80 (62.01%)	594 (66.89%)
Risk factors for DVT		
Age (≥ 70 y)	39 (30.23%)	283 (31.86%)
Cancer	15 (11.62%)	182 (20.50%)
Major surgery*	17 (13.17%)	151 (17.00%)
Major trauma	5 (3.87%)	69 (7.77%)
Cardiovascular and cerebrovascular diseases (e.g., heart failure, stroke)	19 (14.72%)	93 (10.47%)
Immobility (e.g., Air Travel, Paraplegia)	18 (13.9%)	103 (11.59%)
Obesity (BMI>30)	9 (6.97%)	25 (2.81%)
Thrombophilia	1 (0.77%)	25 (2.81%)
HRT, pregnancy related thrombosis	3 (2.32%)	48 (5.40%)
Specific inflammation†	3 (2.32%)	21 (2.36%)
Prognosis		
PTS (6/24 months)	44/81 (34.11%/62.79%)	148/373 (16.67%/32.88%)
Recurring VTE‡	28 (21.7%)	144 (13.06%)
PE	4 (3.10%)	23 (2.59%)
Bleeding complications	13 (10.07%)	149 (16.78%)
Subjects	129 (100%)	888 (100%)

*Major surgery: Patients received major surgery within 1 month. †Specific inflammation: inflammatory bowel disease, sepsis. ‡Recurring VTE: Patients diagnosed with recurring DVT or PE during the follow-up period (regardless of whether in the therapeutic session).

treatment, such as insulin, metformin, etc. The characteristics of the DM and non-DM subgroups were similar in terms of age, gender, blood pressure, and body mass index (BMI) to allow clear assessment of the effects of DM-associated HG. We excluded specific thrombotic risk factors such as elder (322 patients), major surgery (168 patients), malignant diseases (197 patients), major trauma (74 patients), cardiovascular and cerebrovascular diseases (112 patients), thrombophilia (26 patients), hormone replace treatment (HRT) and other prothrombotic diseases (85 patients). In the end, there were 76 DM patients in the DM subgroup and 181 non-DM patients in the non-DM subgroup.

Blood CRP analysis

The level of C-reactive protein (CRP) in blood samples from 257 patients (181 in the non-DM subgroup, 76 in the DM subgroup, following exclusions due to the presence of thrombotic factors as mentioned above) was determined at the time of hospitalization and 2 weeks after anti-coagulation therapy. Blood samples were prepared by centrifugation at 800 g for 15 min and deproteinated. Concentrations of these inflammatory factors were determined with ELISA kits (Sigma-Aldrich, CA, USA) using

matched antibody pairs, according to the manufacturer's instructions. Briefly, samples were added to 96-well plates, incubated at room temperature for 2 h, and then washed 3 times with PBS. After washing to remove the unbound molecules, samples were incubated with 3% bovine serum albumin (BSA) for 30 min to block nonspecific binding. These inflammatory markers were detected by incubation with rabbit anti-rat monoclonal antibody for 1 h, followed by an additional 30-min incubation with horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG. Positive color was developed with o-phenylenediamine and detected using a spectrophotometer (Bio-Rad Laboratories, Hercules, USA) at 450 nm.

Statistical analysis

Data analyses were performed using the SPSS 17.0 statistical software. Patient characteristics are reported as means and standard deviations. Continuous variables are described as medians and quartiles and categorical variables as frequencies and percentages. The median and quartiles of the follow-up distribution were estimated using the Kaplan-Meier method with reverse meaning of the status indicator. Associations between variables were assessed using the independent samples *t*

DM associated HG is a risk for recur DVT & PTS

Table 2. Baseline characteristics of DM vs. non-DM patients

Characteristic	DM† (76)	Non-DM‡ (181)	P
Age (y)	56.1±15.3	52.3±17.1	0.310
Male gender (%)	68.4%	64.6%	0.328
Blood glucose (mmol/L)	10.73±4.60 mmol/L	6.85±2.19 mmol/L	<0.001
HG (%)*	71.0%	10.5%	<0.001
BMI	22.58±1.55	23.27±1.84	0.501
Diastolic blood pressure (mmHg)	81±6.43 mmHg	79±7.18 mmHg	0.359
Recurring VTE (%)	18.4%	9.4%	0.021
PTS (%)	56.6%	32.6%	<0.001

*HG: hyperglycemia, blood glucose ≥ 7 mmol/L. †DM subgroup: excluding specific thrombotic risk factors, only with DM.

‡Non-DM subgroup: excluding specific thrombotic risk factors and DM. Specific thrombotic risk factors, including elder, major surgery, malignant diseases, major trauma, cardiovascular and cerebrovascular diseases, thrombophilia, HRT and other inflammatory prothrombotic diseases.

test, Pearson Chi-Square test or Wilcoxon rank sum test (depending on the distribution of the data). Patient characteristics and DM were entered into multivariate logistic regression models to identify variables that independently predicted risk factors for recurrence in DVT patients. A *p* value less than 0.05 was considered significant.

Results

Study population

During the 10-year study period, 1,214 patients with a first-time diagnosis of lower extremity DVT were admitted to our hospital. One hundred and ninety seven patients were excluded for the reasons listed in **Figure 1**. Hence, 1,017 patients were entered into follow-up and completed the study. The patients' baseline demographic and clinical characteristics are listed in **Table 1**. The median follow-up period was 71.3 months. In our cohort, 129 (12.68%) patients were previously diagnosed with DM. HG status (blood glucose test ≥ 7 mmol/L) was detected in 154 (15.14%) patients (including both DM and non-DM), and HG associated with DM was detected in 60 (5.90%) patients. One hundred and ninety two patients (18.88%) received PTS 6 months after a diagnosis of DVT. The incidence of PTS increased to 373 patients (36.68%) after 24 months. In 144 (14.16%) patients, recurring DVT or PE was diagnosed during the follow-up period. In the DM and non-DM subgroups (**Table 2**), HG was present in 71.0% and 10.5% of patients, respectively ($P < 0.001$).

DM-associated HG is an independent risk factor for recurrence and PTS in patients with DVT

Excluding specific thrombotic risk factors (elder, major surgery, malignant diseases, major trauma, cardiovascular and cerebrovascular diseases, thrombophilia, HRT and other prothrombotic diseases, etc.), the baseline characteristics of DM vs. non-DM patients with a first-time diagnosis of lower extremity DVT are shown in **Table 2**. There were 76 patients in the DM subgroup and 181 in the non-DM subgroup. Fifty-four (71.0%, $P < 0.001$) DM patients were diagnosed with HG, 14 DM patients (18.4%, $P < 0.05$) were diagnosed with recurring DVT/PE, and 43 patients (56.6%, $P < 0.001$) in the DM subgroup suffered PTS during the follow-up period. The *p* values and Kaplan-Meier curves for the recurrence rates of DVT/PE showed significant differences between the DM and non-DM subgroups (recur: $P = 0.021$, < 0.05 ; **Figure 2**). To validate the independent risk factor of recurrence in DVT patients, we performed multivariate analysis for the HR data. **Table 3** shows the multivariable HRs associated with the various risk factors. When compared to other major risk factors (such as cancer, HR=2.10, 95% CI: 1.73-3.05, major surgery, HR=1.72, 95% CI: 1.52-2.04, cardiovascular and cerebrovascular diseases, HR=1.47, 95% CI: 0.91-1.77), DM could not be considered a significant independent risk factor (among the whole population, adjusted HR=1.19, 95% CI: 0.88-1.46, $P = 0.132$). However, the recurring risk seemed higher in DM-associated HG, according to the comparison between the DM subgroup with normal blood glucose (adjusted HR=1.38, 95% CI:

DM associated HG is a risk for recur DVT & PTS

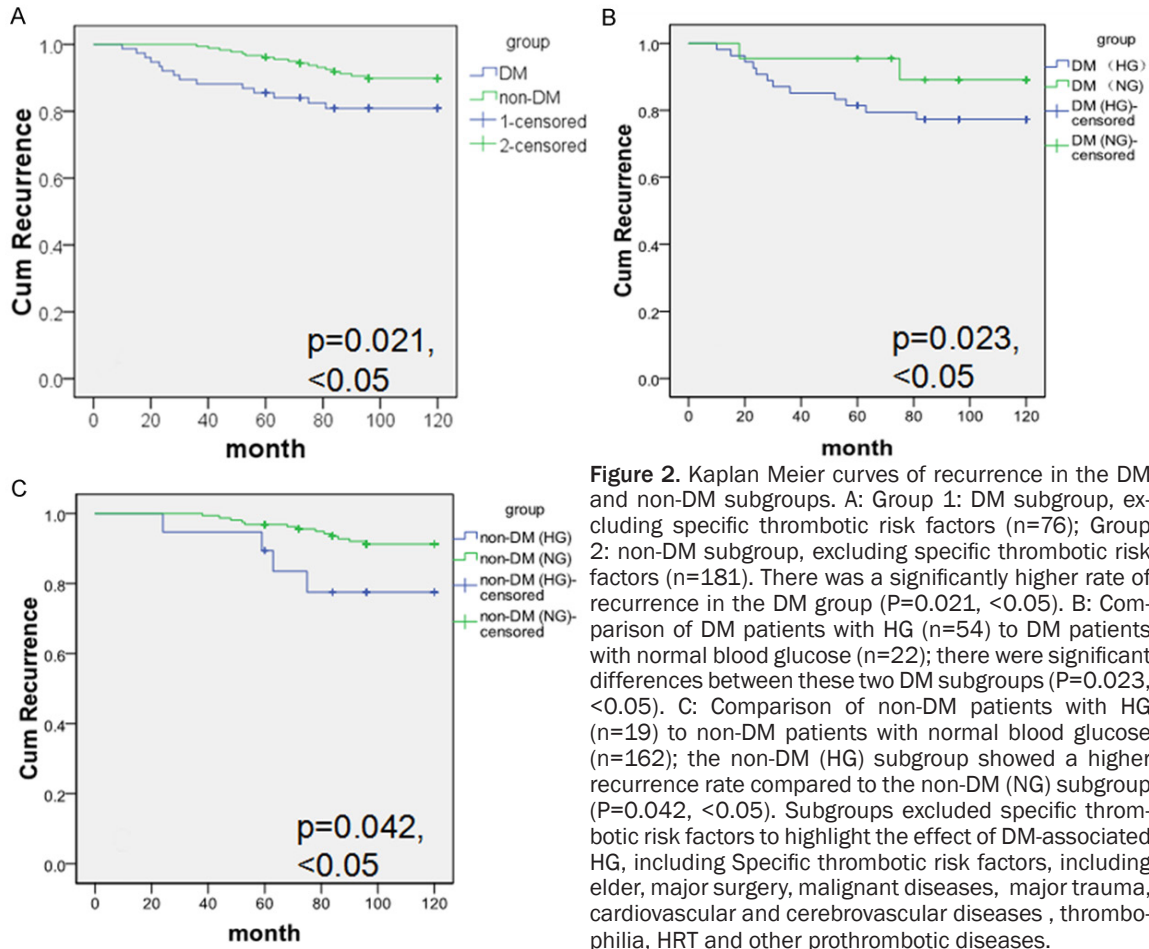


Table 3. Multivariable HRs associated with risk factors of VTE recurrence (cancer, major surgery, cardiovascular and cerebrovascular diseases, DM)

Variable	HR	95% CI	P
Cancer	2.10	1.73-3.05	<0.001
Major surgery	1.72	1.52-2.04	0.007
Cardiovascular and cerebrovascular diseases	1.47	0.91-1.77	0.009
DM	1.19	0.88-1.46	0.132
DM (DM-associated HG vs. DM with normal blood glucose)*	1.38	1.12-1.55	0.010
DM (DM-associated HG vs. non-DM)†	1.34	1.09-1.63	0.025

*DM-associated HG: blood glucose level ≥ 7 mmol/L; DM with normal blood glucose: blood glucose level < 7 mmol/L. †DM-associated HG: blood glucose level ≥ 7 mmol/L; non-DM: not previously diagnosed with DM.

1.12-1.55, P=0.010) and non-DM subgroup (adjusted HR=1.34, 95% CI: 1.09-1.63, P=0.025). These data suggest that DM-associated HG should be considered as an independent risk factor for recurrence. To further investigate whether the level of blood glucose and recurring VTE demonstrate a linear correlation, we used Spearman's linear regression

analysis to determine the correlation coefficient (*r*). We found that there was no linear correlation between blood glucose level and recurring VTE ($r=0.56$, P=0.76). Although our data suggested that DM increased the risk of recurring VTE and PTS and that DM-associated HG was an independent risk factor for recurrence and PTS, there was no significant relationship

DM associated HG is a risk for recur DVT & PTS

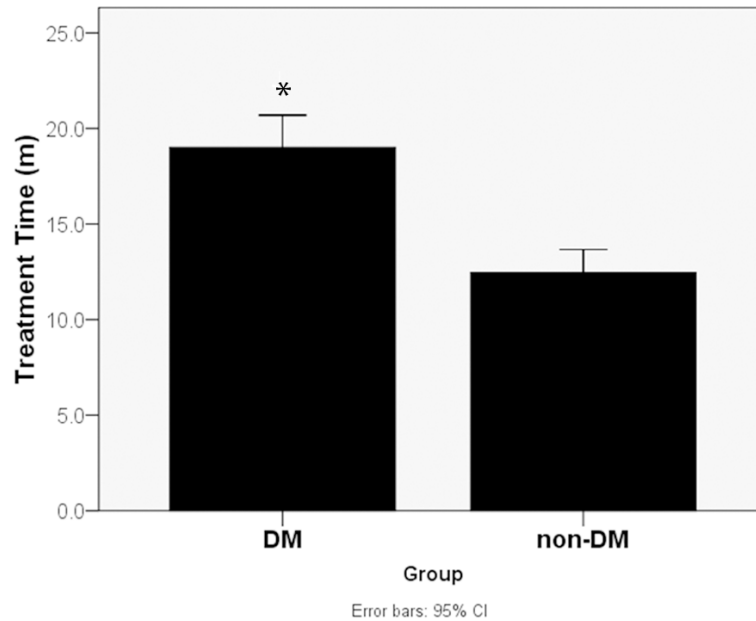


Figure 3. Treatment time (months) in the DM and non-DM subgroups. Average treatment time in the DM subgroup was 19.01 ± 6.51 months compared with 12.47 ± 4.65 months in non-DM subgroup ($P=0.048$, <0.05).

with the blood glucose level and recurring VTE and PTS.

DM-associated HG prolongs the course of DVT treatment

As shown in **Figure 3**, we found that the average treatment duration in DM-associated HG patients was longer than that in non-DM patients without apparent persistent risk factors during the follow-up period (19.01 ± 6.51 vs. 12.47 ± 4.65 months, $P=0.048$, <0.05). Furthermore, 12 months after the diagnosis of DVT, the rate of re-patency (stenosis $<50\%$) of DVT in DM patients was 61.8% (48 in 76), which was lower than that in the group with apparent intermittent risk factors (83.4%; 151 in 181). The p value of the Pearson Chi-Square test was <0.001 ($\chi^2=12.582$). These data suggest that DM-associated HG prolongs the course of DVT and lowers the rate of venous re-patency.

DM-associated HG prolongs thrombotic inflammation in acute DVT patients

Previously, a prospective clinical trial found that acute phase inflammation increased the risk of post-thrombosis syndrome in DVT patients [27]. Thus, we hypothesized that the mechanism underlying recurring VTE associated with

DM-associated HG was likely correlated with the presence of thrombotic inflammation. In the current study, we detected the serum levels of CRP in the DM (76) and non-DM (181) subgroups. As shown in **Figure 4**, we found that, before treatment, the CRP levels in the DM-associated HG group were not significantly different between non-DM patients and DM patients with normal glucose (CRP: $P=0.835$, $P>0.05$). However, after 2 weeks of anti-thrombotic therapy, the level of CRP in the DM with HG group decreased less rapidly than in the other two subgroups, specifically among non-DM patients and DM patients with normal blood glucose (CRP: $P=0.012$, $P<0.05$). These data suggest that DM-

associated HG prolongs acute thrombotic inflammation.

Discussion

This cohort study is the first to demonstrate that DM-associated HG increases the risk of recurrent VTE and PTS, prolongs treatment duration and induces persistent injury due to inflammation associated with acute DVT. These results suggest that, in DVT patients, HG with DM is a poor prognostic factor, potentially due to persistent thrombotic inflammation with a high level of CRP.

Previously, some investigators found HG status to be a prothrombotic factor, resulting from the upregulation of fibrinolysis and coagulation markers, such as plasminogen activator inhibitor-1 (PAI-1), tissue factor (TF), and platelet activation [28, 29]. Accordingly, polymorphisms in the genes encoding PAI-1 and platelet endothelial cell adhesion molecule 1 (PECAM-1) have been shown to influence the degree of thrombus resolution after DVT and the subsequent rate of PTS and could therefore help in predicting the risk of PTS [30, 31]. Izuahara et al. [30] showed that increased expression of PAI-1 in vessel walls shifts the balance between thrombosis and fibrinolysis,

DM associated HG is a risk for recur DVT & PTS

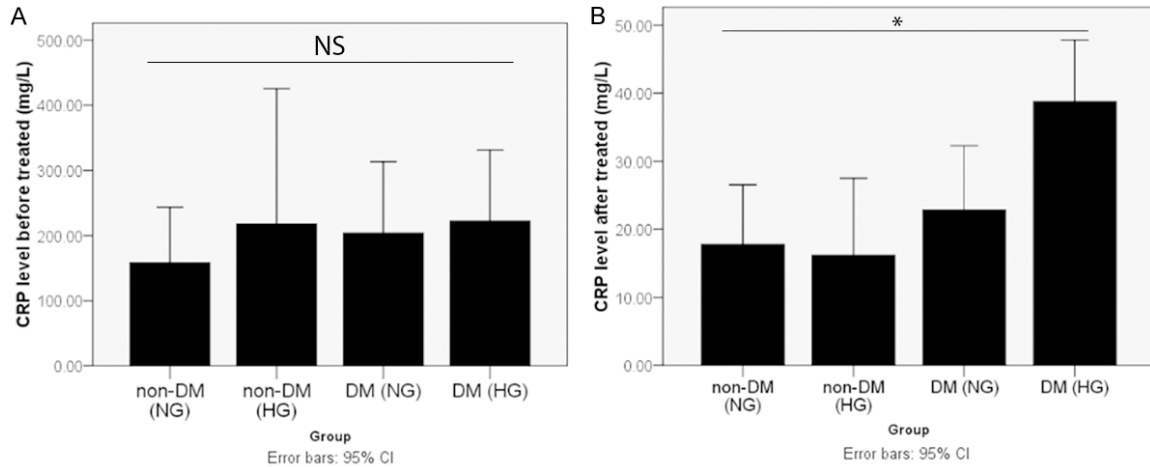


Figure 4. CRP levels in non-DM patients with normal blood glucose, non-DM patients with HG, DM patients with normal blood glucose, and DM patients with HG. A: CRP level (mg/L) in non-DM (NG), non-DM (HG), DM (NG), and DM (HG) patients before anti-thrombotic therapy; there were no significant differences among the four subgroups (non-DM (NG) 158±181 mg/L vs. non-DM (HG) 217±375 mg/L vs. DM (NG) 204±247 mg/L vs. DM (HG) 222±398 mg/L, $P=0.868$, >0.05); B: CRP levels in non-DM (NG), non-DM (HG), DM (HG), and DM (N) patients after anti-thrombotic therapy (2 weeks); the CRP level decreased less rapidly in the DM (HG) group compared to the non-DM and DM (NG) subgroups. There were significant differences among the four subgroups (non-DM (NG) 17±18 mg/L vs. non-DM (HG) 16±20 mg/L vs. DM normal glucose 22±21 mg/L vs. DM-associated HG 39±33 mg/L, $P=0.012$, <0.05). Non-DM (NG): non-DM patients with normal blood glucose, excluding specific thrombotic risk factors; non-DM (HG): patients with hyperglycemia, excluding specific thrombotic risk factors; DM (NG): DM patients with normal blood glucose; DM (HG): DM patients with hyperglycemia.

especially in insulin-resistant DM patients. Moreover, persistent HG increases insulin synthesis and the expression of PAI-1, a mediator of inflammation. Several clinical studies have examined the association between levels of inflammatory markers and venous thrombosis, and the results showed a two- to six-fold increase in the risk of DVT associated with elevations in plasma levels of CRP, interleukin (IL)-6, IL-8, monocyte chemoattractant protein (MCP-1) or tumor necrosis factor (TNF)-alpha [32, 33]. In our study, we found that the HG status in DM patients increased the incidence of recurrence and PTS, indicating that DM-associated HG may play a role in incomplete thrombus clearance (re-patency) and thrombotic inflammation (CRP). These results further suggest that DM-associated HG is a poor prognostic factor in DVT patients. In addition, the results of HR analysis and the persistent level of CRP showed that blood glucose levels below 7 mmol/L reduced the risk of recurrence by reducing inflammatory damage during the acute phase of thrombosis. However, the relationship between DM-associated HG and PTS is not fully elucidated, and prospective studies are needed to confirm that blood glucose con-

trol in DM patients plays a role in the development of PTS.

In recent years, clinicians have paid more attention to vessel wall injury during the course of DVT and have suggested that endothelial dysfunction is a critical factor in determining the incidence of PTS [34, 35]. However, anticoagulation agents that are used clinically (such as LWMH, warfarin, rivaroxaban, etc.) and recommended for the treatment of DVT focus on thrombus formation and offer little protection against endothelial injury. Some investigators have shown in animal studies that diet-induced type 2 diabetes may increase vein wall collagen, with less uPA and more PAI-1 expression, and may increase the expression of MMP-2 and MMP-9 responses thereby impairing DVT resolution [17]. If patients have an indication for catheter-directed thrombolysis (CDT), the incomplete thrombus clearance and incidence of PTS may improve in the early stages. However, extended CDT is associated with an increased risk of bleeding, and stenting of residual venous obstruction is associated with early rethrombosis. Furthermore, the endothelial injury may still exist following the thrombus

attachment to the vein wall [36]. Although DM is not a contraindication to CDT, HG-induced endothelial injury and the refractory balance between thrombosis and fibrinolysis may increase the risk of bleeding complications. Therefore, CDT should be used with caution in DM patients. To date, there has been no clinical trial comparing the effect of CDT therapy and its associated complications in DM and non-DM DVT patients. In a randomized controlled trial, even compression stocking treatment has been challenged due to the lack of satisfactory outcomes in preventing PTS [37, 38]. In particular, compression stocking treatment cannot improve the thrombotic inflammatory insult to the vessel wall. Based on both previous studies and the current study, the link between DM-associated HG, prolonged treatment duration and lower re-patency, resulting from persistent thrombotic inflammation, may impair thrombus resolution and exacerbates endothelial injury. Thus, control of blood glucose is important in reducing the incidence of PTS in patients with DM-associated HG, although the mechanisms are likely complex and difficult to identify.

Targeted therapy with new antithrombotic and anti-TNF-alpha drugs likely represents a threshold of hope in DVT therapeutics [39, 40]. Recent studies have shown that neutrophil extracellular trap (NET) should play a key role in the thrombotic inflammation [41]. Joshi et al. suggested that high glucose has a close relationship with NET [42]. NET should be influenced by hyperglycemia homeostasis, and activated pro-inflammatory condition in neutrophils leading to reduced response to external stimuli making diabetic subjects susceptible to infections. This should be one of the mainly reasons for the diabetes patients have high risk of PTS in DVT.

Conclusion

In conclusion, although the relationship between DM-associated HG and PTS has not been fully elucidated, our results suggest that DM-associated HG increases the rate of recurrence and PTS, increases the HR of recurrence, prolongs the treatment duration and thrombotic inflammation associated with DVT, and lowers the re-patency of the thrombotic vessel. These results support the hypothesis that DM-associated HG is a poor prognostic factor in determining the outcome of DVT.

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Disclosure of conflict of interest

None.

Authors' contribution

Conception and design: YZ, SW; Analysis and interpretation: YZ, YS, RY, NS; Data collection: YS, RY, FP; Writing the article: YZ, NS; Critical revision of the article: YL, SW; Final approval of the article: YZ, YS, RY, NS, FP, YL, SW; Statistical analysis: RY, NS; Obtained funding: YZ, SW; Overall responsibility: SW.

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DM associated HG is a risk for recur DVT & PTS

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