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Incidence of deep vein thrombosis in patients with diabetic foot ulcers

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ABSTRACT

The mortality in type-II diabetes mellitus (T2DM) patients relates to the occurrence of thrombosis events in the peripheral vascular, one of which, diabetic foot ulcers (DFU). Theoretically, an increased tendency for thrombosis in patients with DFU will increase the incidence of thrombosis in the lower limbs that are part of the venous thromboembolism, also known as deep vein thrombosis (DVT). This research was a descriptive study, with a cross-sectional design, aimed to investigate the incidence of DVT in DFU patients in Haji Adam Malik Central General Hospital Medan from September to November 2017. A total sample of 45 patients diagnosed as T2DM with DFU, was selected to join the study based on the inclusion and exclusion criteria. All subjects were asked for their consent before being included in the study. The data collected included patients' personal information, complete diagnosis, hemostatic laboratory results, and doppler USG examination. All data were statistically processed using SPSS software. The results showed that the incidence of DVT in DFU patients was 93.3% based on physical and radiological examination using doppler USG.

Keywords: Diabetes mellitus, diabetic foot ulcers, infection, deep vein thrombosis
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INTRODUCTION

Hyperglycemia, hyperinsulinemia and insulin resistance in type-2 diabetes mellitus (T2DM) have been proven in various research papers to cause changes in the hemostatic system. T2DM patients have been reported to have platelets that are hypersensitive to aggregation impulses. It was also found that there is a tendency of an increased fibrinogen level, von Willebrand factor, factor VII, factor VIII, plasmin activator inhibitor-1 level and a decrease in tissue plasminogen activator (tPA) and prostacyclin level (PGI_2). These changes in the hemostatic system cause an increase in the fibrinolysis activity, making T2DM patients to experience a hypercoagulability state, in which the blood is more vulnerable to clot and lead to thrombosis.[1] The higher tendency of thrombosis in T2DM patients often lead to one of the most common complications found, diabetic foot ulcers (DFU). Thrombosis has become one of the causes of a higher morbidity and mortality in diabetic foot ulcers (DFU) patients. Disruption in the vascularization of the wounded area of the foot becomes the main pathogenesis manifesting as gangrene. Thrombosis will impede the blood flow that supplies nutrition, oxygen, and drugs to the tissue. This disruption in the perfusion causes tissue death, thus making it easier for bacteria to grow and develop in the necrotic tissue. As time passes by, amputation would be one of the solution every DFU patients would have to choose.[2]

The thrombosis events start from disruption in the vascular wall due to erosion or tear of the atherosclerotic plaque. This event triggers the activation of coagulation leading to the forming of a new thrombus. Prado Dos Santos, et al found that 66,7% of DFU patients in their study had undergone major amputation and the rest of them had undergone minor amputation. The amputations were all due to a history of peripheral arterial disease, such as DVT.[3] In a research conducted by Carr ME et al in 2004, it was found that there was an increase in various clotting factors in the blood of diabetes mellitus patients. It was reported that the clotting factors mainly affected the intrinsic pathway including the kallikrein, von Willebrand factor, factor VIII, factor IX, factor XII, as well as the extrinsic pathway, thrombin factor, and factor VII.[4]

Dahlback B at al found that the natural anti-coagulant activity (antithrombin III, protein C dan protein S) was found lower in the T2DM patients compared to healthy individuals. The decrease

activity of antithrombin III would increase the activity of thrombin. Meanwhile, the decrease activity of protein C and protein S would increase the activity of factor V and VIII. All these changes would then lead to hypercoagulability state, which led to another thrombus formation.[5]

Venous thromboembolism occurs because of predisposing factors (genetic and or environment). The combination of one or more of these factors increases the possibility of thromboemboli. The pathogenesis of VTE is attributed by three factors that are related to each other as explained by The Virchow's Triad: (1) The imbalance in hemodynamic system (stasis of blood), (2) disruption in the endothelial vascular wall, and (3) local or systemic hypercoagulability.[6]

Theoretically, an increased tendency for thrombosis in patients with DFU will increase the incidence of thrombosis in the lower limbs that are part of the VTE of DVT. The presence of infection will also affect the occurrence of thrombus. Therefore, researchers in this study were interested in assessing the incidence of DVT in T2DM patients who have experienced DFU at Haji Adam Malik Hospital Medan to do comprehensive management. This study's long-term aim was to reduce the morbidity and mortality of diabetic patients with complications.

METHODS

Study Population

The study was conducted at the Haji Adam Malik Central General Hospital, approved by the Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara. The target population was T2DM patients who had DFU. The affordable population was all DFU patients who visited Haji Adam Malik Central General Hospital from September to November 2017 that met the criteria determined. All patients who were under the age of 18, pregnant women, had malignant comorbid disease, or used oral or injection of anticoagulant drugs during the study were excluded from the study. We collected data from the DFU patients' medical records and from several direct examinations upon subjects. The data obtained were the sociodemographic information, complete diagnosis of the patients including duration of diabetes, and the length of time the patient had taken medications. We performed several examinations, which included complete hemostatic assays taken from the patients' blood samples and doppler USG examination to diagnose DVT. The laboratory assays were done in the Laboratory of Clinical Pathology, Haji Adam Malik Central General Hospital.

Diabetic Foot Ulcers

The manifestation of foot ulcer on T2DM patients was assessed using the Wagner's Criteria for diabetic foot ulcer. The Wagner's criteria for diabetic foot ulcer consist of :

- Grade 1: Superficial diabetic ulcer
- Grade 2: Ulcer extension
  - o Involves ligament, tendon, joint capsule or fascia
  - o No abscess or osteomyelitis
- Grade 3: Deep ulcer with abscess or osteomyelitis
- Grade 4: Gangrene to portion of forefoot
- Grade 5: Extensive gangrene of foot

Hemostatic Assays

Aside from routine blood assays, we also performed hemostatic assays to evaluate the hypercoagulability state on each subject. These blood assays include complete blood platelet count, aPTT, PT, TT, fibrinogen level, and D-dimer. The blood was said to be in a hypercoagulability state if :

- aPTT ratio < 0.8 times control
- PT ratio < 0.8 times control
- D-dimer level > 500 ng/l
- Fibrinogen level > 400 mg/dl

Deep Vein Thrombosis

Diagnosis of deep vein thrombosis included thorough assessment in history, physical examination and several laboratories and radiological assays. In this study, we collected information of patients' history on symptoms related to DVT such as pain and discomfort in the calf, warmth, erythema, and swelling. We performed Doppler USG on the large vessels of the leg to find signs of thrombosis. The frequencies used for the Doppler USG were 3-5 MHz on the iliac vein with a convex transducer and 5-10 MHz on the distal femoral vein with a linear transducer. The diagnosis of DVT was made based on the D-dimer assay and the result of Doppler USG. If the D-Dimer showed a negative result, then the diagnosis of DVT was taken out. If the D-dimer showed a positive result, it indicated for doppler USG to be carried out. If the doppler USG result was negative, the patient was not diagnosed with DVT. In contrary, if the result was positive, then the patient was diagnosed with DVT.

Statistical Analysis

All data were analyzed using SPSS software. The baseline characteristics of the study population were presented in descriptive distribution tables. Data were presented as mean ± standard deviation (SD) or n (%).

RESULTS

This study needed 45 subjects as samples based on the calculation of minimum sample size. We collected the samples from T2DM patient visits to the Clinic of Internal Medicine in Haji Adam Malik Hospital from September to November 2017 that met the inclusion criteria. Out of 45 samples, 24 were male patients (53.3%), and 21 were female patients (46.7%). The age distribution was mostly 51-60 years old (51.1%), with a mean age of 54.9 years (SD 7.82).

The mean value of aPTT was 2 seconds (SD 5.1), with a minimum value of 0.72 seconds (2.2%) and a maximum value of 37.1 seconds (2.2%). The mean value of PT was 2.27 seconds (SD 3.54), with a minimum value of 0.78 seconds (2.2%) and a maximum value of 13.9 seconds (2.2%). The mean value of TT was 2.27 seconds (SD 4.73), with a minimum value of 0.71 seconds (2.2%) and a maximum value of 23.2 seconds (2.2%). The mean value of INR was 1.17 (SD 0.39), with a minimum value of 0.76 (2.2%) and a maximum value of 3.5 (2.2%). The mean fibrinogen level was 501.53 mg/dl (SD 218.7), with a minimum level of 54 mg/dl (2.2%) and a maximum level of 900 mg/dl (4.4%). The mean value of D-dimer was 1356.80 (SD 1947.51), with a minimum level of 105 (2.2%) and a maximum level of 9999 (2.2%).

On Doppler USG examination, we found 42 out of 45 subjects (93.3%) who showed a positive result for DVT and only 3 subjects (6.7%) showed negative DVT results.

Table 1 **Baseline characteristics of the study population ***

Parameter	N=45
Sex n(%)	
Female	21(467%)
Male	24 (53.3%)
Age (years)	
Mean ± SD	54.98 ± 7.82
40-50 n (%)	13 (28.9%)
51-60 n (%)	23 (51.1%)
61-70 n (%)	7 (15.6%)
71-80 n (%)	2(4.4%)
Laboratory Assays	
Mean ± SD	
Hb (g/dL)	10.01 ± 2.24
Ht (%)	29.95 ± 5.55
WBC ($10^3/\mu L$)	13937.40 ± 8623.31
PLT ($10^3/\mu L$)	406291.11 ± 301023.48
aPTT (second)	2 ± 5.1
PT (second)	2.27 ± 3.54
TT (second)	2.27 ± 4.73
INR	1.17 ± 0.39
D-Dimer (Ng/ml)	1356.80 ± 1947.51
Fibrinogen (mg/dl)	501.53 ± 218.17

*Data was presented as mean ± SD or *n* (%) Hb= Hemoglobin, Ht = hematocrit, WBC = White Blood Cells, PLT=Platelets, aPTT = activated partial thromboplastin time, PT=prothrombin time, TT = Thrombin Time, INR = International normalized ratio

Table 2 **USG Doppler Examination**

Doppler USG	Frequency n (%)
DVT	42 (93.3%)
Non-DVT	3 (6.7%)

DISCUSSION

Out of all the T2DM patients treated at the Clinic of Internal Medicine in Haji Adam Malik Hospital from September to November 2017, 45 patients had diabetic foot ulcer complication. The incidence of DVT was obtained by the formula of DVT diagnosed patients treated at RSUP Haji Adam Malik Medan (42 respondents) divided by the number of T2DM patients with DFU (45 respondents), multiplied by 100%. The incidence of DVT in DFU patients in this study was 93.3%.

The D-Dimer assay, which was one of the primary component to asses patients with DVT, was found to be high in most of the subjects in the study. There was a two-fold increase from the normal value of less or equal as 500 ng/ml. This result showed that hypercoagulability in the blood of DFU patients played an essential role in the pathogenesis of DVT. The incidence of infection in DFU was also believed to increase the risk for the formation of a thrombus in the bloodstream and increase the incidence of DVT. This study showed more than 50% of subjects with leukocytosis with a mean value of 13937.40 x $10^3/\mu L$ (SD 8623.31).

The results of this study showed that the DVT case rate was high in cases of DFU. Based on research conducted in the United States, DVT was proven to be an important factor that contributed to reducing the rate of healing in DFU. Smoking history and history of DVT were found as the two most affecting factors that decreased the likelihood of wound healing. Patients with DVT history were found to be 87% less likely to heal (OR 4 0.13, 95% CI0.04–0.42).[7]

More research with bigger sample size is needed to obtain data on factors that directly affect the worsening and healing in DFU patients of getting DVT. By obtaining the risk factors, comprehensive management can be done towards T2DM patients with DFU.

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REFERENCES

1. Meigs JB, et al. Hyerinsulinemia, Hyperglicemia and Impaired Hemostasis. JAMA 2000 ; 283 (2) : 221-8
2. Grant P J. Is hypercoagulability an issue in arterial trombosis? Yes. Journal of Trombosis and Haemostasis 2004 ; 2 : 690 – 1.
3. Dos Santos VP, Da Silveira, Caffaro R A,. Risk Factors for Primary Amputation in Diabetic Patients. Sao Paulo Medical Journal 2006 ; 124 (2) : 66 – 70
4. Carr M E. Diabetes mellitus A hypercoagulable state. Journal of Diabetes and Its Complications 2001 ; 15 : 44 – 54Rauwerda J A. Acute Problems of Diabetic Foot. Acta Chir belg 2004;104 : 140-7.
5. Dahlback B, Villoutreix BO. Regulation of blood coagulation by the protein C anticoagulant pathway: novel insights into structure-function relationships and molecular recognition arterioscler. Thromb Vasc Biol 2005;25: 1311-20
6. Shbaklo H, Kahn S, Long-term prognosis after deep venous trombosis. Hematology. 2008;15:494-8
7. Jagadish M et al. Diabetic Foot Ulcers: The importance of Patient comorbidity recognitionand total contact casting in succesful wound care. The American Surgeon. 2016; 82 : 733-736