HYPERTENSION AND DIABETES MELLITUS ARE ASSOCIATED WITH DEEP VENOUS THROMBOEMBOLISM: A CASE CONTROL STUDY

S.P Ogundeji, F.A Fasola, T.R Kotila

Department of Haematology, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Correspondence:
Dr. T.R Kotila
Department of Haematology,
University College Hospital,
Ibadan, Nigeria
Email: tkotila@com.ui.edu.ng

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ABSTRACT

Introduction: **Identifying risk factors for venous thromboembolism (VTE) is useful in deciding thromboprophylaxis for VTE. A retrospective study had shown an association between hypertension and diabetes mellitus with VTE in our population. The objective of this study was to confirm these findings and to determine if the complete blood count and coagulation tests can also be useful parameters in stratifying VTE patients for prophylaxis.**

Methods: **This is a gender and age matched prospective case-control study of 45 Doppler's confirmed DVT and 43 apparently healthy controls.**

Results: **Identified risk factors included history of hypertension, diabetes mellitus, previous DVT, recent surgery, recent trauma, malignancy, sepsis, and immobility. The cases had a significantly lower mean haematocrit (33±7.4% vs 38±4.6%, p<0.001). Though no differences were observed in leucocyte and platelet counts between cases and controls but stratification as leucocytosis vs leucopaenia (P=0.003) and thrombocytosis vs thrombocytopaenia (P=0.045) differed between both groups. Also, the International normalized ratio (INR) was higher in cases (1.1±0.2 vs 1.0±0.1; *P*=0.001), hypercoagulable state (INR<0.9) and hypocoagulable state (INR>1.2) were observed in 4.4% and 28.9% of cases respectively but not in controls (*P*<0.001). Also, aPTT>40 seconds was seen in 4.4% vs 4.7% of cases and controls respectively and aPTT< 30 seconds in 22% of cases but not in controls (*P*=0.004).**

Conclusion: **Hypertension and diabetes mellitus are identified risk factors not traditionally associated with DVT. These in addition to a complete blood count and coagulation tests can be useful in stratifying patients for prophylaxis in our population and other similar communities.**

Keywords: Anaemia, Diabetes mellitus, Hypercoagulable, Hypocoagulable, Hypertension, Race, Thromboprophylaxis

INTRODUCTION

Venous thromboembolism (VTE) affects 1-3 patients per 1000 years.[1,2] One percent of all hospitalized patients die of acute pulmonary embolism (PE) and 10% of all in-patient deaths are PE related.[3] The pathogenesis of VTE is complex and includes both hereditary and environmental factors.[4] Though anaemia was found to be independently associated with the risk of VTE in acutely ill medical patients[5] there appears to be no demonstrable relationship between it and PE.[6] However, there is a relationship between platelet counts and the rate of major and fatal bleeding in patients with VTE.[7] Reactive thrombocytosis is also found to be a risk for venous thromboembolism during the recovery phase of an acute illness.[8] Recently, it was observed that comorbidities like hypertension and diabetes mellitus appear to be associated with VTE in our population of patients in a retrospective study.[9] We therefore sought to identify comorbidities and laboratory parameters that are associated with VTE in our community. This can be useful in deciding the requirements for thromboprophylaxis in hospitalized patients in our population and similar communities.

MATERIALS AND METHODS

Study Design: This was a gender and age matched (±3 years of index case) prospective case-control study of consecutive patients with deep venous thromboembolism.

Setting: The study was carried out in a 964 bedded tertiary health facility in a cosmopolitan city in Nigeria. Study Population: The cases were in-patients confirmed to have deep venous thrombosis by ultrasonography. Patients with established renal failure and inheritable risk factors like deficiency of Protein C, Protein S, antithrombin, resistance to activated protein C as documented in the case notes were excluded from the study. Also, excluded were pregnant women or women with a history of recent childbirth. The body mass index was calculated from the weight

and height of the participants (weight (kg)/height (m)^2, a BMI of 25-30kg/m^2 was considered overweight while a BMI of >30kg/m^2 was considered obese. The controls were apparently healthy individuals who work in and around the hospital and consented to participate.

Variables: The outcome variable is deep venous thrombosis which was confirmed by Doppler ultrasonography. The risk factors were obtained using an interviewer administered questionnaires and laboratory blood samples which were processed by automation.

Sample size: The estimated sample size of 45 was based on a significance threshold of 0.05, a statistical power of 80%, prevalence of 20%[10] and attrition rate of 5%. Prevalence from our community was 2.9%[11] giving a sample size of 37.

Sample Collection: After an informed consent, a questionnaire detailing the risk factors was administered to all participants. Blood samples were collected and dispensed into bottles containing EDTA for complete blood count and trisodium citrate for prothrombin time (PT) and activated partial thromboplastin time (aPTT). Platelet poor plasma was obtained from the sample collected into trisodium citrate bottle after centrifugation at 3000g for 15 minutes. The PT and aPTT were run manually immediately after separation. The complete blood count was determined by automation using a five- part particle counter by Sysmex 1000*i*.

Anaemia was classified as haematocrit (PCV) of less than 36% while a count of greater than 51% was classified as polycythaemia, other readings were considered normal. Leucopaenia was a leucocyte count of less than 4.0 x 10^9/ L, while counts greater than 10.0 X 10^9/L were considered as leucocytosis and values between 4.0 x 10^9/ L and 10.0 X 10^9/L were considered normal. Platelet count of between 100 X 10^9/L and 300.0 X 10^9/L was considered normal, values below were classified as thrombocytopaenia and values above as thrombocytosis. The international normalized ratio was calculated by dividing the PT of the patient by that of the control plasma multiplied by the international sensitivity index (ISI) of the thromboplastin used. INR within the range of 0.9 and 1.2 was considered normal, values above were classified as hypocoagulable and values below as hypercoagulable. The reference ranges used for the complete blood count parameters and the coagulation profile were based on that of our laboratory.

Statistical consideration and Data analysis: Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 16. Descriptive variables were summarized as mean and SD for continuous variables and as numbers and percentages for categorical variables. Frequency distribution tables were generated for the different variables while cross-tabulations and test statistics for bivariate analysis were carried out as applicable; independent t test was used to compare continuous variables and Chi square test for categorical variables. Level of significance was set at a *P*-value of less than 0.05.

Ethical Consideration: Ethical approval for the study was obtained from the UI/UCH institutional review board (UI/EC/10/0203). An informed consent was obtained from all participants before the commencement of the study. Privacy and confidentiality of the participants were ascertained by the coding of the data to ensure anonymity.

RESULTS

A total of 88 individuals participated in the study, this included 45 patients and 43 apparently healthy controls. The mean age of the cases and controls were 57.2±17.9 years and 54.5±15.8 years respectively. There were no significant differences between the age and gender of both groups. A higher proportion of the patients were either overweight or obese compared to the control (57.8% vs 46.5%; *P*=0.29) respectively). There was a significant difference in the history of hypertension, diabetes mellitus, previous DVT between patients and controls while there was no significant difference in the history cigarette smoking and family history of DVT between the two groups. Sepsis, malignancies, recent surgery or trauma were documented in the patients and attained statistically significant difference between cases and controls (Table 1).

Table 1: Bivariate analysis of association with deep venous thrombosis

Risk Factors	Cases n (%)	Controls n (%)	P value
Age (mean±sd)	57.2±17.9	54.5±15.8	0.978
Male	23(51.1)	15(34.9)	0.124
Female	22 (48.9)	28(65.1)	
Hypertension	21 (37)	4 (9.3)	<0.001
Diabetes mellitus	8 (17.8)	0	0.004
Cigarette smoking	3 (0.07)	0	0.08
Recent surgery	6 (13.3)	0	0.013
Recent trauma	6 (13.3)	0	0.013
Family history of DVT	2 (4.4)	0	0.16
Previous DVT	5 (11.1)	0	0.02
Overweight/obesity	26 (57.8)	20 (46.5)	0.29
Malignancy	17 (37.8)	0	<0.001
Sepsis	11 (24.4)	0	0.001
Immobility	24 (53.3)	0	<0.001
Congestive cardiac failure	2 (4.4)	0	0.16

The cases had a significantly lower mean haematocrit than the control group (33±7.4% vs 38±4.6%, p<0.001). Among the cases, 73.3% were classified as having anaemia in comparison to 27.9% of the controls (Table 2). There was no significant difference between the mean leucocyte (83.3± 39X10^9 /L vs 73.1± 23.139X10^9 /L, p= 0.55) and platelet counts (286± 139 39X10^9 /L vs 275±9739X10^9 /L, p=0.67) between patients and controls respectively. Leucocytosis occurred in 31.1% of cases compared to 4.7% of controls, similarly, thrombocytosis was seen in 15.6% of cases and 4.7% of controls (Table 2).

observed in 4.4% vs 4.7% of patients and controls respectively but hypercoagulable state (aPTT< 30 seconds) was observed in 22% of patients but in none of the controls. However, the mean aPTT did not differ between patients and controls (31.3±5.5 vs 32.2±3.2; *P*=0.53).

DISCUSSION

Risk factors associated with DVT in this study included history of hypertension, diabetes mellitus, previous DVT, recent surgery or trauma, sepsis and malignancy. Anaemia, leucocytosis and thrombocytosis were

Table 2: A comparison of the complete blood count between cases and controls

Complete Blood Count	Study Group (N=45)	Control (n=43)	Total (n=88)	P Value
Haematocrit				
Anaemia	33(73.3)	12(26.6)	45(51.1)	
No Anaemia	12(27.1)	31(72.1)	43(48.9)	<0.001
WBC				
Leucopaenia	1(2.2)	0	1(1.1)	
Normal	30(66.70	41(95.3)	71(80.7)	
Leucocytosis	14(31.1)	2(4.7)	16(18.2)	0.003
Platelet Count				
Thrombocytopaenia	3(6.7)	0	3(3.4)	
Normal	35(77.8)	41(95.3)	76(86.4)	
Thrombocytosis	7(15.6)	2(4.7)	9(10.2)	0.045

WBC: White blood cell count

Though the mean prothrombin time did not differ significantly between cases and control (14.5±2.6 vs 13.8±1.0; *P*=0.6)), cases had a significantly higher international normalized ratio (INR) than controls (1.1±0.2 vs 1.0±0.1; *P*=0.001). INR of <0.9 (hypercoagulable state) and hypocoagulable state (INR>1.2) was observed in 4.4% and 28.9% respectively of cases but none of the controls were hypercoagulable or hypocoagulable (Table 3). Also, based on activated partial thromboplastin time (aPTT), hypocoagulable state (aPTT>40 seconds) was

haematological parameters that were associated with DVT while prolonged INR and shortened aPTT (hypercoagulable state) were coagulation profile associated with DVT. Hypertension and diabetes mellitus which were not traditionally classified as risk factors for VTE have therefore been found consistently in association with VTE in our population.[9] Cancer associated thrombosis (CAT) which is now considered an entity was found in 37.8% of the patients, a three-fold increment in the prevalence found previously in the retrospective study.[9]

Table 3: Coagulation profile of DVT patients and apparently healthy control

Coagulation parameters	Study group (n=45)	Control Group (n=43)	Total (n=88)	P Value
INR				
Hypercoagulable	2(4.4)	0	2(2.3)	
Normal	30(66.7)	43(100)	73(83)	
Hypocoagulable	13(28.9)	0	13(14.4)	<0.001
APTT				
Hypercoagulable	10(22.2)	0	10(11.4)	
Normal	33(73.4)	41(95.3)	74(84.1)	
Hypocoagulable	2(4.4)	2(4.7)	4(4.5)	0.004

INR: International normalised ratio; APTT: Activated partial thromboplastin time

There are controversies about hypertension and diabetes mellitus as risk factors for VTE. Some studies have shown association[12,13] while others have shown no association[14,15,] others have gone further to show protective effect of both cardiovascular risk factors.[16,17] We believe these differences might be due to racial factor, findings in our study which was conducted in a homogenously African population agreed with a previous study in the same population.[9] The studies which showed association between hypertension and diabetes mellitus and VTE were carried out in non-Caucasian populations.[12,14,18] while those showing association were conducted in populations which were mostly Caucasians.[14,15] Systematic reviews have also shown non association between VTE and hypertension and diabetes mellitus[19,] and the observed association thought to be largely due to the effect of BMI.[15,16,20] However, BMI in our study did not differ between cases and control showing that the association is unlikely to be mediated through BMI. Again, a systematic review done mostly in non-Caucasian population sustained the association between VTE and hypertension and diabetes mellitus.[21]

Anaemia, leucocyte and platelet counts were also observed to be associated with VTE in our study. Though there are controversies between anaemia and venous thromboembolism. The controversy however, appears to revolve around pulmonary embolism rather than DVT[6,22,24] and the patients in our study did not include patients with PE. The association my therefore be genuine. Lymphocyte and neutrophil counts were not only found to be associated with VTE but in addition neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were found to be independent risk factors for VTE.[18] A complete blood count can therefore be useful in identifying patients with the risk of VTE. This is particularly useful in low resource country where these tests can equally be readily available.

Hypercoagulability evidenced by a shortened aPTT is independently associated with the risk of VTE[24,25] a finding that was confirmed in this present study. Though, in our study and the previously cited studies, aPTT was determined after the patients had developed VTE. A longitudinal study which collected risk factors and baseline aPTT sustained the association between baseline aPTT and long-term risk of VTE, suggesting that aPTT could be a coagulation test associated with the pathophysiology of thrombosis.[26] Similarly, aPTT was found to predict cancer patients likely to develop central venous catheter related VTE[27] and recurrence of VTE after withdrawal of anticoagulation.[28] The finding of a prolonged INR rather than PT in association with VTE in our study will therefore suggest the usefulness of INR rather than PT in patients with VTE. In low income setting like ours, a shortened aPTT rather than PT could therefore be used as a possible predictor for the development of VTE in hospitalized patients.

The strength of this study is that it was done in a homogenously African population. The limitations are the small sample size and the choice of a healthy population as control. The association of history of hypertension and diabetes mellitus with VTE in this study may not be generalizable to other communities, especially since they may be genetically determined. Hypertension and diabetes mellitus as risk factors for VTE may therefore differ between Caucasians and Africans.

CONCLUSION

The association of hypertension and diabetes mellitus with VTE is not confounded by BMI in this present study as seen in Caucasian populations compared to non-Caucasian populations. The controversies on the association between these cardiovascular risk factors may therefore be due to racial differences.

Authors contributions: FF and TK conceptualized the study, PO designed the study, collected and analyzed the data. TK and PO prepared the initial draft. All authors approved the final draft.

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