ORIGINAL ARTICLE

APTT: A Screening Test For Hypercoagulability in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Thrombosis is a common complication in Type 2 Diabetes Mellitus (T2DM). Prolonged APTT values have clinical relevance as an indicator of factor deficiency or the presence of coagulation inhibitors. However, there is mounting evidence that shortened APTT values in some cases may reflect a hypercoagulable state, which is potentially associated with increased thrombotic risk and adverse cardiovascular events. We set out a cross-sectional study to measure the haemostatic profiles of T2DM patients and to determine the suitability of PT-APTT as markers for hypercoagulability in T2DM patients using VWF as a gold standard.

Methods: PT, APTT, VWF and Fibrinogen concentrations were measured in 213 T2DM patients and 172 non-diabetic healthy participants. VWF was used as a proxy marker for hypercoagulability in T2DM patients. Participants with VWF of >2.0 IU/ml , PT and APTT less than 11 and 30 seconds respectively, were regarded as being in hypercoagulable state.

Results: The results revealed that mean fibrinogen concentration for T2DM patients (4.3 ±2.5g/l) was significantly higher than control participants (2.3±1.6 g/l); P-value = 0.003.The mean Vonwillebrands factor concentration for T2DM patients (7.4 ±4.1 IU/ml) was significantly higher than control participants (2.6±2.2 IU/ml). P-value = 0.0004. The mean Prothrombin Time for T2DM patients (12.4±3.3 seconds) was lower than control participants (12.5 ±2.9 seconds) but the difference was not significant P-value = 0.168. The mean APTT for T2DM patients (24.7 ±3.8seconds) was significantly lower than control participants (32.2±4.2seconds). P value = 0.000. The study further revealed that APTT tests were more sensitive 93.7% (95% CI [88.0-96.7)] than PT test which had a sensitivity of 55.6% (95% CI [46.8-63.9)]. Both APTT and PT tests had better specificity; however APTT was higher 95.4% (95% CI [88.8-98.2]) than PT test 90.8% (95% CI [82.9-94.3]). APTT test had a higher PPV 96.7% (95% CI [91.9-98.7)] than PT test 89.7% (95% CI 81.0 94.7]). PT test gave a much lower NPV 58.5% (95% CI [50.0-66.5]) as compared to APTT tests which had a higher NPV 91.2% (95% CI [83.6-94.5]).

Conclusion: Haemostatic profile results show that T2DM patients are more hypercoagulable than non-diabetic healthy individuals. APTT had a better diagnostic specificity and sensitivity than PT. It is cheaper, easier to do and has high PPV and NPV compared to PT. APTT could therefore be used as a marker for hypercoagulability in T2DM patients.

INTRODUCTION

Thrombosis is the leading cause of morbidity and mortality in patients with diabetes mellitus. Eighty percent

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of patients with diabetes mellitus die due to thrombosis, and 75% of these deaths are due to cardiovascular complications (1). At Ndola Central Hospital (NCH) more than 50% of patients admitted for cardiovascular complications, have T2DM. (2).

Several mechanisms contribute to diabetic prothrombotic state. These include endothelial dysfunction, coagulative activation and platelet hyper-reactivity. In particular, diabetic platelets are characterized by deregulation of several signalling pathways leading to enhanced adhesion, activation and aggregation (3). These alterations result from the interaction between hyperglycemia, insulin resistance, inflammation and oxidative stress. The prothrombotic or hypercoagulable state is not easily detected by routine laboratory tests unlike the hypocoagulable state. So far, no coagulation screening test is available to detect a hypercoagulable state, whether it is due to congenital or acquired thrombotic disorders, with the exception of lupus anticoagulant (LA). In hypocoagulable state, APTT is a useful screening test in the investigation of bleeding disorders. Prolonged APTT and corrected result after mixing test is most likely to be associated with hypocoagulable disorder due to coagulation factor(s) deficiency (4).

Although modern coagulation diagnostic tests are becoming more sophisticated, standard coagulation screening tests, such as activated partial Thromboplastin time (APTT) and Prothrombin time (PT) are still important basic examinations in clinical laboratories. APTT is commonly used to test the intrinsic coagulation pathway; whereas prolonged APTT is a clinical indicator of either a factor deficiency or the presence of coagulation inhibitors (5). The APTT assay is traditionally used for identifying abnormalities in the contact (factor XII, prekallikrein, and high-molecular-weight kininogen), intrinsic (factors XI, VIII, IX) and common (factors X, V and II and fibrinogen) pathways of coagulation (6). Prolonged APTT values have clinical relevance as an indicator of factor deficiency or the presence of coagulation inhibitors. However, there is mounting evidence that shortened APTT values in some cases may reflect a hypercoagulable state, which is potentially associated with increased thrombotic risk and adverse cardiovascular events (5,7). Shortened APTTs may result from an accumulation of circulating activated coagulation factors in plasma caused by enhanced coagulation activation in vivo (5,7).

From the literature searched so far no studies were found that have explicitly evaluated PT and APTT as markers of hypercoagulation in terms of Sensitivity, Specificity, Positive and Negativity predictive values. This is the first study to evaluate PT and APTT as markers of hypercoagulation in T2DM patients. Soltan et al., (2011) and Lip et al., (2010), have shown Von Willebrands and fibrinogen to be predisposing factors for thrombotic development in T2DM patients and have been widely used as markers for hypercoagulability in T2DM patients (8,9). However most assays designed to estimate plasma von willebrands factor concentration are very expensive and tedious to perform and hence cannot be done routinely in most laboratories in Zambia. The total cost of analyzing a sample for vonwillebrands factor is about 30 US dollars, while the cost of PT, APTT and Fibrinogen test is less than 3 US dollars per sample. Though fibrinogen is comparable to PT and APTT in terms of cost, it is also an acute phase protein hence can increase in other inflammatory conditions, thus making it a non-specific marker for hypercoagulation (10). There is no data available regarding haemostatic profile and prevalence of hypercoagulability among Type 2 Diabetes Mellitus patients in Zambia. Many of the previous studies on haemostatic changes in diabetic Patients have been conducted in Europe and Asia. Currently in Zambia, haemostatic profile tests are not part of tests done in the management of T2DM patients. Furthermore the prognosis is not good when diabetic patients suffer from cardiovascular or cerebrovascular thrombotic diseases. Early detection of the prothrombotic state is therefore critical for the administration of preventive therapy in T2DM patients. Therefore inclusion of the haemostatic tests in the management of T2DM patients will result in commencement of early treatment in those patients suspected to be in hypercoagulable state and hence reduction of deaths occurring as a result of thrombosis.

It was therefore cardinal that a study was done to determine hypercoagulability status of T2DM patients and evaluate PT and APTT as markers for

hypercoagulability using VWF as a gold standard. This is very vital; especially that PT and APTT can easily be done in most laboratories as these tests are cheaper to perform and reagents are readily available.

The aim of this study was to measure the haemostatic profile of T2DM patients and evaluate the suitability of PT-APTT as markers for hypercoagulability state in T2DM patients using vWF as a gold standard.

MATERIALS AND METHODS

This study was conducted at Ndola Central Hospital, a third level referral hospital for Copperbelt and Northern part of Zambia. It is located in Ndola, the provincial headquarters of the Copperbelt Province. The hospital has a bed capacity of 851.

The study was a cross-sectional descriptive study involving T2DM patients attending Ndola Central Hospital Out-patient Department (OPD) Diabetic clinic and healthy adult male and female participants visiting OPD for medical examinations between November 2012 to May 2013. The total number of participants recruited in this study was 385. This included 213 T2DM patients and 172 healthy adult individuals as control participants.

Convenience sampling was used to recruit 213 T2DM patients and 172 non-diabetic healthy controls attending medical examinations at Ndola Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria

The study included male and female T2DM patients and Non-diabetic healthy individuals above the age of 18 years.

Exclusion criteria

Participants who had a history of venous thromboembolism or known inherited coagulation disorders, Cancer and hyperthyroidism were excluded from the study. Others excluded include, those who were Pregnant, had recent surgery, those taking standard anticoagulant treatment, less than 18 years and those not willing to consent.

Data collection

Good Laboratory Practice (GLP) principles according to the Ministry of health laboratory quality manual was observed to ensure uniformity, consistency, reliability and reproducibility of all the laboratory test results produced in this study. Venous blood collection was done by using the evacuated blood collection system. 3 ml of venous blood was collected for each test. Three (3) ml of venous blood for PT and APTT was collected from each of the study participants in sodium citrate containers and centrifuged at 1500g for 15 minutes. Plasma was then separated and transferred into siliconized glass tubes and stored at 4C in a fridge until analysis. The reagents used for PT and APTT were sourced from SPINREACT Diagnostics Company of Spain. PT and APTT results were reported in seconds. Any participants' PT and APTT results which were below 11 seconds and 30 seconds respectively were considered as being hypercoagulable state.

Blood for fibrinogen determination was collected from the study participants in sodium citrate containers and centrifuged at 1500g for 15 minutes. Plasma was then separated and transferred into plastic or siliconized glass tubes and stored at -20C until analysis. The reagents for this test were sourced from SPINREACT Diagnostics Company of Spain.

The kit used utilizes the thrombin clotting time assay based on the method originally described by Clauss (11). The reference range for fibrinogen concentration was taken as 1.6 to 3.2 g/l. Any participants' fibrinogen result above 3.2 g/l concentration was regarded as hypercoagulable state.

The same participants' plasma samples for PT and APTT analysis as prepared above was also used for vWF analysis. VWF was determined by the Human ELISA kit manufactured by Abnova of USA. Plasma VWF concentration results were reported in International units/ml (IU/ml).The reference range for plasma concentration of vWF is 0.6 to 2.0 IU/ml. Any result above 2.0 IU/ml was regarded as being in hypercoagulable state.

Sensitivity, Specificity, Positive and negative Predictive values for PT and APTT as markers for

hypercoagulability were determined. VWF concentration was used as a proxy standard method for hypercoagulability and this was compared to PT and APTT results for each patient. The cross tabulation tables obtained from SPSS between VWF results in comparison to PT/APTT were transferred to CEBM (Center for evidence Based Medicine) Statistics Calculator for calculation of sensitivity, specificity, positive and negative predictive values.

Ethical considerations

This study was performed under a protocol that was reviewed and approved by the University of Zambia-Biomedical Research Ethics Committee (UNZA-BREC). Written permission was obtained from the Permanent Secretary in the Ministry of Health as well as from the Senior Medical Superintendent of Ndola Central Hospital. All the prospective participants in this study were informed about the study, privileges and right to participation. The purpose of the study was thoroughly explained to the participants and those that declined to participate in the study were not forced, but were assured of their protected privileges and rights to treatment. Privacy and confidentiality was maintained. The names of the respondents did not appear anywhere on the forms instead codes were used on the forms. The forms were kept in lockable cabinets and no one apart from the researcher had access to the cabinets. Data on the computer was pass-word protected such that access was limited to only the researcher. Consenting patients and control participants were made to sign the consent form before being enrolled into the study.

Data analysis

The Statistical Package for Social Science (SPSS version 16) and CEBM Statistics Calculator was used to analyse the results statistically. Analysis of distribution was made using the Kolmogoroff-Smirnoff test. All the parameters were normally distributed and hence reported as the mean +/- standard deviation. The significance of the differences between patients and controls for normally distributed parameters were determined using the independent samples T-test. Sensitivity, Specificity and Positive predictive value for PT-APTT as markers for hypercoagulability were calculated from a 2x2 table computed in CEBM Statistics Calculator. P-values of less than 5% were taken as significant.

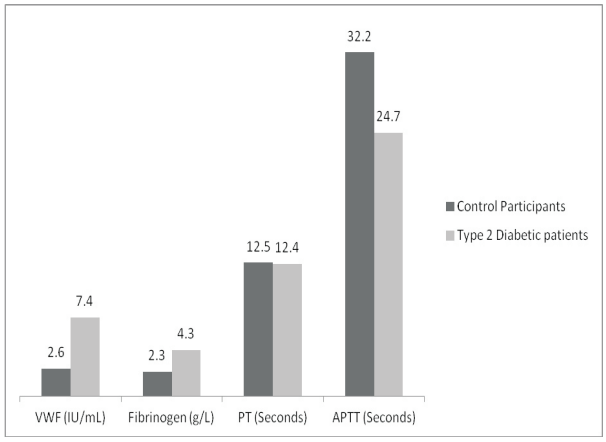
RESULTS

An independent-sample t-test was conducted to compare the haemostatic profiles in T2DM and control participants. Table I and figure I, reveals that mean fibrinogen concentration for T2DM patients (4.3 ±2.5g/l) was significantly higher than control participants (2.3±1.6 g/l); P-value = 0.003.

Table I: Haemostatic profiles in type 2 diabetes mellitus patients and control
Subjects. Independent t-test parameters.

	Status	N	Mean	Std. Deviation	P-value
vWF (IU/mL)	Male	93	2.6	1.2	0.001
	Female	120	4.6	2.3	
Fibrinogen (g/L)	Male	93	3.4	2.0	0.017
	Female	120	4.3	2.4	
PT (Seconds)	Male	93	11.9	3.3	0.172
	Female	120	11.2	2.8	
APTT (Seconds)	Male	93	32.0	3.0	0.001
	Female	120	28.3	3.5	

Figure I: Comparison of mean haemostatic profiles between Type 2 diabetic patients and control participants.



The mean Vonwillebrands factor concentration for T2DM patients (7.4 ±4.1 IU/ml) was significantly higher than control participants (2.6±2.2 IU/ml); P-value = 0.0004.

The mean Prothrombin Time for T2DM patients (12.4±3.3 seconds) was lower than control participants (12.5 ±2.9 seconds) but the difference was not significant; P-value = 0.168.

The mean Activated Partial Thromboplastin Time for T2DM patients (24.7 ±3.8seconds) was significantly lower than control participants (32.2±4.2seconds; P value = 0.000.

Table II and III illustrates the crosstabulations of VWF results in comparison to the PT and APTT test results. Table 4 reveals that 126(59.1%) of the participants were hypercoagulable (had VWF results of greater than 2.0 IU/ml). Out of these results,70(32.9%) participants results were true positives, implying that both the VWF test results and the prothrombin time were abnormal. 8(3.7%) of the results were false positive test results with the prothrombin test but the patients were not hypercoagulable because the VWF results were below 2.0 IU/ml. 56 (26.3%) of the participants results were false negatives, implying that the prothrombin test results were negative but the participants were in actual fact hypercoagulable. 79(37.1%) negative prothrombin test results were true negatives because the VWF results were also positive, implying that the patients were hypercoagulable. Table IV reveals that 118(54.3%), 4(1.9%), 8(3.7%) and 83(39.0%) APTT test results were True Positives, False Positives, False negatives and True Negatives respectively. Table IV reveals that APTT tests were more sensitive 93.7% (95% CI [88.0-96.7)] than PT test which had a sensitivity of 55.6% (95% CI [46.8-63.9)]. Both APTT and PT tests had better specificity; however APTT was higher 95.4% (95% CI [88.8-98.2]) than PT test 90.8% (95% CI [82.9-94.3]). APTT test had a higher PPV 96.7% (95% CI [91.9-98.7)] than PT test 89.7% (95% CI 81.0 94.7]). PT test gave a much lower NPV 58.5% (95% CI [50.0-66.5]) as compared to APTT tests which had a higher NPV 91.2% (95% CI [83.6-94.5]). This entails that APTT is a better predictor of hypercoagulable state than PT in T2DM patients. Furthermore, APTT is a better discriminator for non-hypercoagulable states in T2DM patients.

Table II: Comparison of VWF results and PT test results in type 2 diabetes mellitus patients

PT test	Vonwillebrands factor		
	Hypercoagulable (VWF >2.0 IU/ml)	Normal VWF =2.0 IU/ml	Total
Hypercoagulable	70 **TP**	8 **FP**	78
Normal	56 **FN**	79 **TN**	135
Total	126	87	213

Table III: Comparison of VWF results and APTT test results in type 2 diabetes mellitus patients

APTT test	Vonwillebrands factor		Total
	Hypercoagulable (VWF >2.0 IU/ml)	Normal VWF ≤2.0 IU/ml	
Hypercoagulable	118 **TP**	4 **FP**	122
Normal	8 **FN**	83 **TN**	91
Total	126	87	213

TP: True Positive TN: True Negative FP: False Positive FN: False Negative

Table IV: Quality evaluation of PT and APTT parameters

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PT	55.6	90.8	89.7	58.5
APTT	93.7	95.4	96.7	91.2

DISCUSSION

It was observed in this study that the Prothrombin time (PT) of diabetic subjects (12.4± 3.3 seconds) was insignificantly shorter than that of non diabetic controls (12.5± 2.9 seconds) P= 0.168. Partial thromboplastin time (APTT) in the diabetic subjects was significantly shorter than that of controls (P=0.000). The results for Prothrombin Time accords that of Zhao et al.,(2011) who found insignificant shortened PT in T2DM patients as compared to control subjects (12). The results are also consistent with Lippi et al., (2009), who found shortened PT and APTT in T2DM patients than in non-diabetes control subjects, but only the APTT results were significantly shorter (7). Boekel et al., (2002) reported that PT and APTT tests are standard screening tests for function of the coagulation system and their utility in

monitoring therapeutic anticoagulation is widely accepted (13). Prolonged APTT values have clinical relevance as an indicator of factor deficiency or the presence of coagulation inhibitors. Shortened APTTs are generally considered to be laboratory artifacts arising from problematic venepunctures. However, there is mounting evidence that shortened APTT values in some cases may reflect a hypercoagulable state, which is potentially associated with increased thrombotic risk and adverse cardiovascular events (5,7). Shortened APTTs may result from an accumulation of circulating activated coagulation factors in plasma caused by enhanced coagulation activation in vivo (5,7).

Acang et al., (2005) observed that there were significantly shortened PT and APTT values, in diabetic patients, especially in patients with long-term diabetes with chronic complications, which are consistent with the results of this study ((14). The insignificant PT results support the hypothesis that there is less involvement of the extrinsic pathway in hypercoagulability state in diabetic conditions due to the fact that injury occurring to the vascular system in diabetic patients does not involve tissue factor from outside the vascular system (8). Korte et al. (2008) reported that patients presenting with shortened APTT values had increased thrombin generation, were in a complex hypercoagulant state and were at increased risk for thromboembolism(15). Tripodi et al. (2004) found that hypercoagulability detected by shortened APTT values was independently associated with venous thromboembolism (VTE) and hypothesized that shortened APTT could be considered as a risk marker for VTE (6).

The mean fibrinogen concentration of persons with diabetes in this study was significantly higher than the concentration in the controls ($P < 0.05$). This higher fibrinogen concentration found in the diabetic group agrees with Mark's report (2001) of elevated fibrinogen concentration as one of the risk factors for atherosclerosis among diabetics (16). The findings also accords that of Zhao et al., (2011) who reported increased Fibrinogen concentrations among Chinese T2DM patients (12). Fibrinogen may induce thrombus formation by affecting platelets and erythrocytes to aggregation and by promoting increased blood viscosity (17). Kannel et al., (2005) reported that fibrinogen is often elevated in T2DM patients and this elevation is associated with poor glycaemic control (18). The increase in fibrinogen levels in T2DM patients may be due to chronic fibrinogen synthesis. Increased fibrinogen levels in diabetes may be related to the associated low-grade inflammation. Interleukin (IL)-6 levels are elevated in diabetes and this cytokine is able to stimulate hepatocytes to produce fibrinogen, representing an important link between inflammation and hypercoagulation. In an hyperglycemic environment, fibrinogen can become hyperglycosylated, when this abnormal fibrinogen clots, the resulting fibrin structure is composed of small diameter fibers that are markedly resistant to degradation by plasmin hence increase in hypercoagulability (12).

In the current study, the mean von willebrands factor concentration was higher in T2DM patients (7.4 ± 4.1 IU/ml) than the control participants (2.6 ± 2.2 IU/ml). This accords the results obtained by Mohamed et al., (2005), who found increased VWF levels in T2DM patients than control participants (19). The findings also correlates with Alzahrani et al., (2010), who found elevated VwF concentrations in T2DM patients as compared to non-diabetic control participants (20). Soltami et al., (2011) also obtained elevated vWF in T2DM patients than the control subjects (8). VWF is also known as a marker for endothelium damage and in turn is increased in T2DM patients (21,22,23). VWF is produced by endothelial cells and megakaryocytes throughout the body (24). Levels of circulating vWF are increased following endothelial cell damage. Several mechanisms contribute to the endothelial dysfunctional phenotype in T2DM patients including altered glucose metabolism, impaired insulin signalling, low-grade inflammatory state, and increased reactive oxidant species (ROS) generation. Enhanced oxidative stress in the hyperglycaemic milieu accelerates the glycoxidation of proteins and lipids to generate advanced glycation end products (AGEs) (25). AGEs accumulate in the vessel wall, where they may directly disturb cell structure and function and hence exposure of the vWF which is always found in the sub endothelium layer. The mean Fibrinogen and Vonwillebrands factor were significantly increased in Female T2DM patients than in male patients. P-values 0.017 and 0.001 respectively.

The study revealed that PT test had more false negative results which culminated in a much lower sensitivity 55.6% (95% CI [46.8-63.9)] than the APTT test which had low False negative results and hence a better sensitivity of 93.7% (95% CI [88.0-96.7)] This implies that the PT test is only capable of detecting 55.6% of hypercoagulable cases among T2DM patients and therefore 44.4% of the cases will be missed as these will be regarded as negative while in the actual fact they are positive cases. On the contrary APTT test had a better sensitivity of 93.7% (95% CI [88.0-96.7)]. This implies that the APTT test is capable of detecting 93.7% of hypercoagulable cases among T2DM patients and only 6.3% will be missed as these will be reported as negative. Therefore APTT tests have higher probability of detecting hypercoagulable states in T2DM than PT test.

Both APTT and PT tests had acceptable specificity. However APTT had a higher specificity 95.4% (95% CI [88.8-98.2]) than PT test 90.8% (95% CI [82.9-94.3]). This implies that the probability of T2DM patients who were not truly hypercoagulable and gives normal APTT and PT results was 95.4% and 90.8% respectively. Which means only 4(4.6%) and 8(9.2%) tests gave false positive test results for PT and APTT respectively.

APTT test had a higher PPV 96.7% (95% CI [91.9-98.7)] than PT test 89.7% (95% CI 81.0-94.7]). This can be interpreted to mean that 118(96.7%) and 70(89.7%) positive APTT and PT test results respectively were truly hypercoagulable cases.

PT test results had a very low NPV of 58.8% as compared to APTT tests which had 91.2%. This means 79(58.8%) of negative PT test results were true negatives (not hypercoagulable) while 56(41.1%) were False Negatives (Hypercoagulable). From the literature searched so far, no diagnostic study has been done to specifically evaluate suitability of PT and APTT in detection of hypercoagulable states among T2DM patients. Loog T.W (2003) reported that the acceptable sensitivity, PPV and NPV should be above 90% (26). From the results obtained in this study APTT was found to be a suitable screening test for hypercoagulability in T2DM patients because all the parameters were above 90%. Though PT had acceptable specificity, the test is not suitable for use as a screening test for hypercoagulability in T2DM patients because it had very low sensitivity and negative predictive values. This entails that APTT is a better predictor of hypercoagulable state than PT in T2DM patients. Furthermore, APTT is a better discriminator for non-hypercoagulable states in T2DM patients.

Positive and negative predictive values vary according to the prevalence of the condition under study (26). Therefore it would be wrong for predictive values determined for one population to be applied to another population with a different prevalence. In this case APTT tests could only be used among T2DM patients and not the general population because hypercoagulability may be very low in the population and hence low predictive values even if the test is highly sensitive and specific.

There are limitations with APTT test, for example possible pre-analytical errors that could occur during venepuncture procedure or during sample collection. Inappropriate blood taking procedure may lead to coagulation factors activation and falsely giving a shortened APTT results. Other problem with APTT is the consistency in reporting the results. The coagulation laboratory should practice an appropriate quality procedure, including accuracy and precision testing, participation in internal and external quality assurance programme, establishment of a normal reference ranges and other related requirements.

Validation process should be done regularly whenever changes occur in the reagents (including lot number), equipments and etc. Laboratories running APTT and other haemostatic tests should follow the standard guideline for coagulation study to avoid errors (pre-analytical, analytical and post analytical) by practicing a regular auditing, considering the use of uncertainty of measurement in the results reporting (or when consulted) and verifying the correct normal reference ranges for local use. By doing this, the finding of shortened APTT can be recognized consistently in cases with high coagulation factors or due to other reasons that can contribute to this effect. Ability to detect the evidence of hypercoagulable state through this test is strictly dependent on the laboratory performance in their practice.

CONCLUSION

T2DM patients had shorter APTT-PT and higher fibrinogen and VWF than the healthy non-diabetic control participants contributing to increased prevalence of hypercoagulability in diabetic patients than control participants. APTT could be used as a marker of hypercoagulability in T2DM patients because it is economical, easier to perform, very sensitive, specific and have high Positive and Negative Predictive Values.

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DEFINITIONS

Hypercoagulability- Abnormality of blood coagulation that increases the risk of thrombosis.

Sensitivity ("positivity in disease") refers to the proportion of participants who have the target condition (reference standard positive) and give positive test results.

Specificity ("negativity in health") is the proportion of participants without the target condition and give negative test results.

Positive predictive value is the proportion of positive results that are true positive (i.e. have the target condition) whereas negative predictive value is the proportion of negative results that are true negatives (i.e. do not have the target condition).

ABBREVIATIONS USED

APTT: Activated Partial Thromboplastin Time; **CEBM**: Center for Evidence Based Medicine; **NCH**: Ndola Central Hospital; **NPV**: Negative Predictive Value;

OPD: Out Patient Department; **PPV**: Positive Predictive Value; **PT**: Prothrombin Time;

ROS: Reactive Oxygen Species; **T2DM**: Type 2 Diabetes Mellitus; **TF**: Tissue factor; **UNZA-BREC**: University of Zambia Biomedical Research Committee;

VWF: Vonwillebrand's factor.

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