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# Evaluation of Prothrombin time and Activated Partial Thromboplastin Time Tests in Diabetes Mellitus Patients at Meru Teaching and Referral Hospital

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**Abstract**
**Introduction:** *Diabetes mellitus is a chronic and a progressive disease. The risk of at herothrombotic complication is increased in diabetics. Research has shown a diverse of Diabetes mellitus related abnormalities especially in haemostasis and thrombosis. The main objective of this study was to investigate the Prothrombin time and Activated partial thromboplastin time in Diabetes mellitus patients.*
**Methodology:** *Descriptive analytical cross-sectional study was employed to recruit 371 participants. Venous blood was collected (4.5 mls) in 3.2% trisodium citrate (0.5 mls) for prothrombin time and activated partial thromboplastin time testing. It was analyzed using coagulation analyzer (Start 4). Capillary blood was used for glucose estimation by glucose oxidase method.*
**Results:** *There was low degree of correlation between prothrombin time, international normalized ratio and activated partial thromboplastin time of diabetics as compared to the controls (R=4%, p=0.215, R=4%, P=0.221 and R=4%, P=0.445 respectively). There was statistical significant in activated partial thromboplastin time in relation to age (p=0.005) with no statistical significant in prothrombin time (0.839) and international normalized ratio (p=0.880).*
**Conclusion:** *Prothrombin time and international normalized ratio were not significantly affected by the diabetic state of the study subjects. Activated partial thromboplastin time had a significant difference in age group means revealing hypercoagulable state. Preventive measures should be undertaken in these age groups to ensure complications associated with hypercoagulable state do not occur.*
**Keywords:** *Prothrombin time, Activated partial thromboplastin time, International normalized ratio, hypercoagulable.*

## Introduction

Diabetes, which is a long term disease condition, leads to an increased blood sugar levels[(1)]. According to Singh[(2)], it is a common endocrine disease is associated with multiple etiologies, presents with chronic hyperglycemia with disturbances in the metabolism of the carbohydrates, fats, and proteins. The excess blood glucose brings about some of major symptoms associated with Diabetes mellitus, such as polydipsia, polyuria and polyphagia[(3).] Diabetes was not a new disease to

Indian physicians even before 1500BC[4]. Diabetes is among the oldest diseases known in human history, it was first reported in Egyptian manuscript approximately three centuries ago[5]. The prevalence of Diabetes mellitus is drastically increasing worldwide and approaching epidemic proportions[6]. In 2013, according to Awad et al,.[1], estimations indicated that over 382 million people worldwide suffered from diabetes. Therefore, about 90% of the diabetic cases are Type 2 Diabetes mellitus while 10% of the cases are Type 1 Diabetes mellitus and so, diabetes is a serious health problem [3]. The risk of atherosclerosis is very high in the diabetics with coronary artery disease being the major cause of death in these individuals [7].

Persistent hyperglycemia in patients with Diabetes mellitus, leads to red cells being exposed to elevated glucose levels, consequently, leading to glycation of several parameters such as haemoglobin, prothrombin, fibrinogen, as well as other proteins involved in clotting mechanisms [3]. Once the intrinsic and extrinsic clotting factors are glycated, the availability of these factors is significantly decreased and it will affect the clotting capacity [3]. Diabetic patients have disturbances of the haemostatic and fibrinolytic mechanisms, with the development of diabetic complications being associated with them, as well as the incidence of cardiovascular events being increased[8]. The main causes of morbidity and mortality in the diabetics result from thrombosis and related complications[7,8]. Several studies have been done in Kenya describing the prevalence of diabetes, none has compared diabetes and its relationship with basic coagulation tests. Therefore, this study aims to compare basic coagulation tests (Prothrombin time and Activated partial thromboplastin time) in Diabetes mellitus.

**Methodology**

The study design used was descriptive analytical cross-sectional study in June 2019 to October 2019. The study population comprised of Diabetic patients in the outpatient diabetic clinic and both males and females were recruited. Study participants were aged below 60 years meeting the inclusion criteria. The sampling technique used was random systematic method to recruit study participants upon consenting and filling consent forms. Those aged below 18 years, consent was sought from their parents or guardians. Ethical clearance was obtained from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH/UoN ERC).

Venous blood was collected (4.5 mls) in 3.2% trisodium citrate (0.5 mls) for prothrombin time and activated partial prothrombin time. One drop of capillary blood was used for blood glucose analysis by glucose oxidase method.

Study data was keyed into MS-EXCEL and analyzed with SPSS version 23. Comparison of haemostatic parameters (Prothrombin time, International normalized ratio, and Activated partial thromboplastin time) between male and females was done by use of independent sample t- test parameters. Linear regression was used to determine the relationship between coagulation parameters (Prothrombin time, International normalized ratio, and Activated partial thromboplastin time) and glucose parameters in diabetic patients. ANOVA was used to evaluate the variation of coagulation parameters in diabetic participants in relation to age. The alpha level was set at 5% ($p<0.05$). The data was presented using tables and graphs.

**Results**

Figure 1 shows a cross tabulation of independent variables of the study participants. A total of 371 diabetic subjects participated in the study. Male subjects were 152 (41%) while female participants were 219 (59%). The age group of the participants ranged from 18-60 years. The age of the participants were grouped into four groups; 18-30 years having 28 (7.5%) participants, 31-40 years with 78 (21%) participants, 41-50 had 123 (33.2%) participants, while 51-60 years had 142 (38.3%) study subjects. Their mean age was 45.99 with a SD of 9.501. The age range was 42 and 48.29 was the median age.

**Figure 1** Demographic Attributes of study Participants

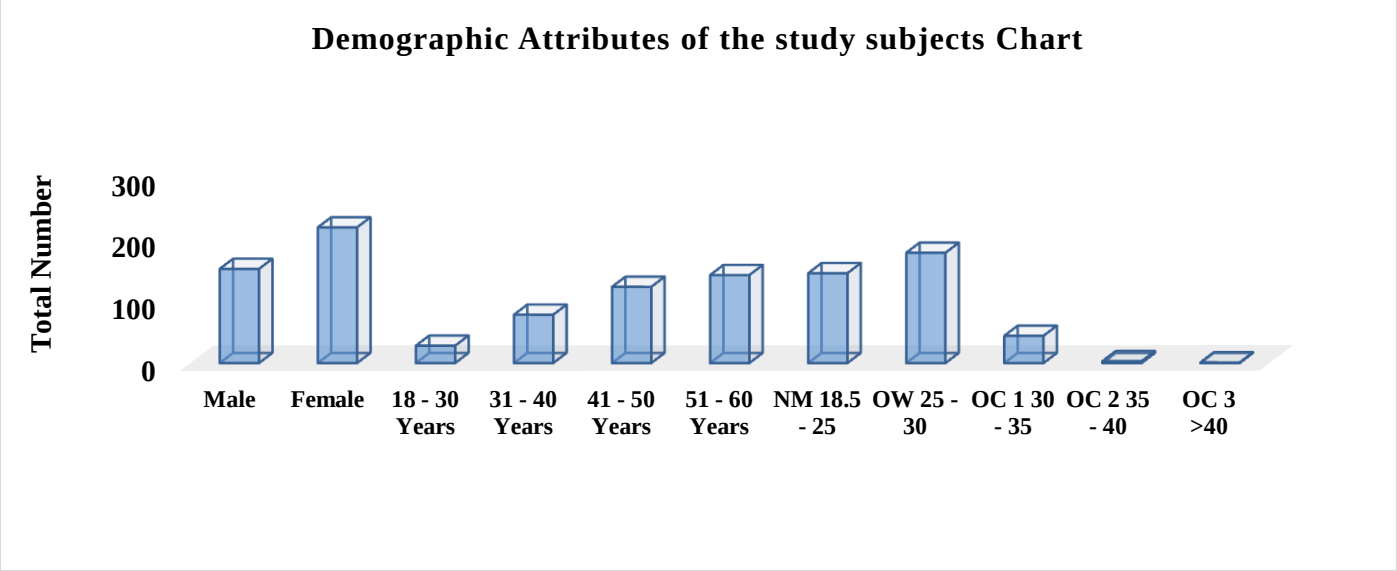


**Table 1** Coagulation Status of Diabetic participants: ***Linear regression***; p-value = <0.05

| Variables | Subjects | Sample | Mean | SD | R | R Square | F-value | *p*-value |
|---|---|---|---|---|---|---|---|---|
| PT | Patient PT | 371 | 12.726 | 1.307 | 0.065 | 0.04 | 1.542 | 0.215 |
| | PT Control | 371 | 12.487 | 1.016 | | | | |
| INR | INR for Patient | 371 | 1.0142 | 0.137 | 0.064 | 0.04 | 1.500 | 0.221 |
| | INR Control | 371 | 0.9891 | 0.102 | | | | |
| APTT | Patient APTT | 371 | 30.656 | 3.74 | 0.04 | 0.002 | 0.586 | 0.445 |
| | | | | | | | | |
| | APTT Control | 371 | 34.424 | 2.71 | | | | |

A linear regression was conducted to determine the relationship of coagulation status in diabetic patients and control samples. **Table 1** shows the means of the two sample groups and their standard deviation, the R value and the p value. The R value of 0.065 indicates a very low degree of correlation between prothrombin time of the diabetic patients and prothrombin time of control samples. The R =0.065=6.5% indicates weak relationship. The mean prothrombin time for the diabetics (12.726±1.3070 seconds) was higher than the prothrombin time control (12.487±1.0157 seconds) but the difference was not statistically significant F-value = 1.542; p-value = 0.215.

The table shows R=0.064 indicating low degree of correlation between patient's international normalized ratio and control INR. R = 0.064=6.4% signifying very weak relationship. It also reveals the mean and the standard deviation for international normalized ratio. The mean international normalized ratio for the diabetics (1.0142±0.13735) was higher than the international normalized ratio of control samples (0.9891±0.10222) but the difference was not statistically significant F-value = 1.500; p-value = 0.221.

The table further reveals the following: R=0.040 indicating low degree of correlation between patient's activated partial thromboplastin time and control activated thromboplastin time. This is 4% signifying very weak relationship indicating that only 4% of the dependent variable has been explained by the independent variable. The mean activated partial thromboplastin time for the diabetics (30.656±3.7374) was lower than that of the activated partial thromboplastin time of controls (34.424±2.711) but the difference was not statistically significant F-value = 0.586; p-value = 0.445.

An independent-sample t-test was conducted to compare the coagulation parameters of diabetic participants according to sex. **Table 2** shows the mean of male prothrombin time (12.8±1.09) was higher than then mean for female prothrombin time (12.7±1.44) but the difference was not statistically significant as the p-value was greater than the threshold value of 0.05 t-value = 0.591; p-value = 0.55.

The mean international normalized ratio for males (1.02±0.11) was higher than the mean for female international normalized ratio (1.01) with no statistical significance t-value = 0.418; p-value = 0.676.The mean activated partial thromboplastin time for males (30.5±3.48) was lower than mean activated partial thromboplastin time for females (30.8±3.91) but the difference was not statistically significance t-value = -0.577; p-value = 0.564.

**Table 2** Comparison of haemostatic parameters of males and females: Independent-sample t-test parameters, *P*-value = < 0.05

| Variable | Sex | Reference range | Total number | Mean | Standard deviation | t-value | P-value |
|---|---|---|---|---|---|---|---|
| Prothrombin time | Male | 10 – 12 Seconds | 152 | 12.8 | 1.09 | 0.591 | 0.55 |
| | Female | | 219 | 12.7 | 1.44 | | |
| International normalized ratio | Male | 0.90 – 1.2 | 152 | 1.02 | 0.11 | 0.418 | 0.676 |
| | Female | | 219 | 1.01 | 0.15 | | |
| Activated partial thromboplastin time | Male | 30 - 40 Seconds | 152 | 30.5 | 3.48 | -0.577 | 0.564 |
| | Female | | 219 | 30.8 | 3.91 | | |

**Table 3** Variation of coagulation parameters in diabetic patients in relation to age: One-way ANOVA Test, *p*-value = < 0.05

| Variable | Age group | Reference range | Total number | Mean | Standard deviation | df | F | P-Value |
|---|---|---|---|---|---|---|---|---|
| International normalized ratio | 18 – 30 | 0.8 – 1.2 | 28 | 1.02 | 0.101 | Between groups = 3 Within groups = 367 | 0.224 | 0.880 |
| | 31- 40 | | 78 | 1.01 | 1.00 | | | |
| | 41 – 50 | | 123 | 1.02 | 0.96 | | | |
| | 51 – 60 | | 142 | 1.01 | 0.185 | | | |
| Prothrombin time | 18 – 30 | 10 – 14 Seconds | 28 | 12.8 | 0.99 | | 0.281 | 0.839 |
| | 31- 40 | | 78 | 12.6 | 1.00 | | | |
| | 41 – 50 | | 123 | 12.8 | 0.97 | | | |
| | 51 – 60 | | 142 | 12.7 | 1.71 | | | |
| Activated partial thromboplastin time | 18 – 30 | 30 – 40 Seconds | 28 | 29.4 | 2.98 | | 4.395 | 0.005 |
| | 31- 40 | | 78 | 31.6 | 3.81 | | | |
| | 41 – 50 | | 123 | 31.0 | 3.57 | | | |
| | 51 – 60 | | 142 | 30.1 | 3.84 | | | |

**Table 3** shows that, at *p*-value < 0.05, the international normalized ratio means between the four age groups as revealed by one-way ANOVA F(3,367) = 0.224, *p* = 0.880.Therefore, there was no statistically significant differences between the group means. The prothrombin time means between the groups as revealed by the one-way ANOVA F (3,367) = 0.281, *p* = 0.839 indicating no statistically significant difference between the groups as presented in table 3.The activated partial thromboplastin time between the groups as revealed by one-way ANOVA F (3,367) = 4.395, *p* = 0.005. The *p*-value 0.005 is below the significance *p*-value 0.05, revealing a statistically significant difference between the group means. Tukey post hoc test was done to determine which specific group differed.

**Table 4** Post HOC Test to determine which specific (APTT) age group differed as seen in **Table 3**: Tukey

| Variable | Age group | Age group | Mean | *P*-value |
|---|---|---|---|---|
| APTT | 18 - 30 | 31 – 40 | -2.1847 | 0.037 |
| | | 41 – 50 | -1.6049 | 0.162 |
| | | 51 - 60 | -0.6455 | 0.832 |
| | 31 - 40 | 18 – 30 | 2.1847 | 0.037 |
| | | 41 – 50 | 0.5798 | 0.698 |
| | | 51 - 60 | 1.5392 | 0.017 |
| | 41 - 50 | 18 – 30 | 1.6049 | 0.162 |
| | | 31 – 40 | -0.5798 | 0.698 |
| | | 51 - 60 | 0.9594 | 0.151 |
| | 51 - 60 | 18 – 30 | 0.6455 | 0.832 |
| | | 31 – 40 | -1.5392 | 0.017 |
| | | 41 - 50 | -0.9594 | 0.151 |

**Table 4** Reveals there was a statistically significant difference between activated partial thromboplastin timein age groups by one-way ANOVA F(3, 267) = 4.395, *p*-value = 0.005. There was a statistically significant difference in activated partial thromboplastin time variation between age groups 18-30 and 31-40 (*p*-value = 0.037), and 31-40 and 51-60 (*p*-value = 0.017).There was no statistical significance in activated partial thromboplastin time variation between age group 18-30 and 41-50 (*p*-value = 0.162), 18-30 and 51-60 (*p*-value = 0.832), 31-40 and 41-50 (*p*-value = 0.698), and lastly 41-50 and 51-60 (*p*-value = 0.151.

**Discussions**

The objective of the study was to evaluate prothrombin time and activated partial thromboplastin time in diabetic patients. Three hundred and seventy one (371) diabetic patients and 371 normal control samples were studied. The majority of diabetic participants were females 219 (59%) while the male participants were 152 (41%). The activated partial prothrombin time of the participants was insignificantly shorter than that of the normal control samples while prothrombin time of diabetic subjects was insignificantly prolonged than that of normal control samples. International normalized ratio was insignificantly increased in the diabetic subjects as compared to normal control samples. This results differs from Mwambungu's[9] who reported significantly reduced activated partial thromboplastin time and insignificantly shortened prothrombin time in diabetic subjects than non-diabetic control participants. This clearly indicated incompetent intrinsic pathway and therefore hypercoagulable state in participants who took part in that study. The prothrombin time in that study was normal indicating a competent extrinsic coagulation pathway, showing adequacy of coagulation factors involved in this pathway. Mwambungu's[9] results were consistent with Ephraim *et al.*, [10] and Awad *et al.*,[1] who reported significantly shortened activated partial thromboplastin time, but their prothrombin time findings differed which was significantly shortened in Ephraim *et al.*,[10] while in Awad *et al.*,[1] report, prothrombin time and international normalized ratio were consistent with the findings of this study with no statistically significant different in the prothrombin time and international normalized ratio of diabetic participants and the healthy participants. The variation in activated partial thromboplastin time and prothrombin time results observed among different researchers could be associated with the sample size used. For example, Ephraim *et al.*, [10] had a small sample size of 100 both diabetic subjects and controls. This may have contributed to the variations observed between this current study and the previous studies. In Mwambungu's[9]study, 213 type 2 diabetic participants participated in the study, which was also less than the sample size used in this study with 19 participants being more than 60 years old. The variation in study variables especially age could have led to the differences in activated partial thromboplastin time, prothrombin time and international normalized ratio in this study

as compared to others. A study done by Agarwal *et al.*,[11] revealed shortened activated partial thromboplastin time and prothrombin time and hence being inconsistent with findings of this study, the reason could be attributed to age of the participants as participants were aged 35 – 70 years while participants in this current study were younger aged 18 – 60 years. In addition, the sample size was smaller, 60 diabetics and 30 controls as compared to this study could have resulted to the disparities between this studies, and the race (Indian race vs African race) as well. According to a study done by Chaitanya and Kavuri[12], their study revealed prolonged prothrombin time and activated partial thromboplastin time in diabetics, which differed from the findings of this study. This implies that the extrinsic and intrinsic pathways were affected and hence the diabetic patients could suffer from excessive bleeding in case of injuries. According to Ogedegbe[13] the activated partial thromboplastin time and prothrombin time prolongation may be associated with factor deficiency or due to circulating anticoagulants. The international normalized ratio findings of this study differed fromEphraim *et al.*, [10]who reported significantly decreased international normalized ratio in diabetics than in non-diabetics. A study done by Dallatu[3] was in agreement with the findings of this current study which revealed that there was no statistically significant difference in treated diabetic participants and the control subjects. Madan *et al.*,[14], found no statistical significance in activated partial thromboplastin time and prothrombin time of both diabetics and non-diabetics just as the findings of this study. Normal prothrombin time and activated partial thromboplastin time could be associated with treatment of diabetics in this study with antidiabetic drugs enabling them have a normal coagulation status.

Female participants were the majority (59%) as compared to men (41%). The prothrombin time, international normalized ratio and activated partial thromboplastin time were within the reference range hence normal. There was no statistically significance difference between the prothrombin time (*p*-value = 0.55) of males and that of females. The international normalized ratio findings (*p*-value = 0.676) had no significant difference between sex. Both mean prothrombin time and mean international normalized ratio in males were insignificantly higher than that of females while mean activated partial thromboplastin time was insignificantly higher in females than in males (*p*-value = 0.564). This current study reveals that activated partial thromboplastin time findings do not correlate with Mwambungu's[9] findings who observed statistically significant low mean activated partial thromboplastin time in females than in males. The prothrombin time was consistent with Mwambungu's[9] findings, which revealed insignificant higher mean prothrombin time in males than in females.

Variation of coagulation parameters in diabetic participants in relation to age was studied. The participants were divided into four (4) age groups. The study observed that there was no significant difference in prothrombin time and international normalized ratio means of the different age groups with a *p*-value of 0.839 and 0.880 respectively. The activated partial thromboplastin time means of different age groups revealed an overall statistically significant difference with a *p*-value of 0.005, which was below the set alpha level (p = <0.05). Post hoc test was done to determine which specific group differed.

The post hoc test (Tukey) revealed that there was significant different in the means of 18 – 30 and 31 – 40 age groups with a mean difference of 2.18 and a *p*-value of 0.037. The group means difference of 31 – 40 and 51 – 60 age groups was 1.54 with a *p*-value of 0.017 which was significant. A study done by Mwambungu[9]revealed that diabetic subjects aged 51 years and above were at risk of being hypercoagulable as compared to those below 51 years of age, this was in line with the findings of this study as the diabetic subjects in the age group 51 – 60 years had their activated thromboplastin time statistically significant indicating hypercoagulable state. According to Mwambungu[9],

changes occurring to the vascular system as the age increase could be associated with hypercoagulation status. This indicates abnormalities in the intrinsic and common pathways of the coagulation cascade [15]. There was no significant difference in the means of groups 31 – 40 and 41 – 50, 41 – 50 and 18 – 30, 41 – 50 and 51 – 60, 51 – 60 and 18 – 30 ($p>0.05$).

**Conclusions**

This study revealed that the extrinsic pathway of coagulation was intact in diabetics with hypercoagulable state in different age groups indicating incompetence of the intrinsic coagulation pathway. Preventive measures should be undertaken in these age groups to ensure complications associated with hypercoagulable state do not occur.

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