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Prothrombin Time, Activated Partial Thromboplastin Time and Plasma Fibrinogen Concentration among Alcoholics in Sokoto, Nigeria

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List of abbreviations
ALD- alcohol liver diseases
APTT- Activated Partial Thromboplastin Time
CHD- coronary heart disease
HCC- hepatocellular carcinoma
PAI-1- plasminogen activator inhibitor-1
PT- Prothrombin time
vWF - von Willebrand
WHO- World Health Organization

Abstract
The aim of the study was to determine Prothrombin time, Activated partial thromboplastin time and plasma fibrinogen concentration of alcoholics in Old Airport, Sokoto, Sokoto State. Six millilitres (6.0mls) of venous blood were collected into trisodium citrate containers from the subjects for the estimation of PT and APTT using Agape Diagnostics reagents from Switzerland GmbH, while the plasma obtained was used for the estimation of fibrinogen concentration using Ingram technique. The results were presented using tables in mean ± standard deviation. The result obtained showed a significant increase in the PT and APTT ($p<0.05$) and a significant decrease in fibrinogen concentration (FC) of subjects ($p<0.05$) of the alcoholics compared with the controls. There was a significant increase in PT and APTT ($p<0.05$), and a significant decrease in fibrinogen concentration ($p<0.05$) of heavy consumers compared with moderate consumers. The study also showed a significant increase in PT in relation to age ($p=0.033$). There was significant increase in PT and APTT of the alcoholics in Sokoto. Also, PFC decreased in alcoholics in Sokoto. The study concludes that moderate consumption of alcohol does not have haemostatic effect but heavy consumption does. Therefore PT, APTT and PFC should be included in routine test to monitor patients with alcohol related disorders to avoid possible haemostatic disorders.

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Introduction

Alcohol is any organic compound in which the hydroxyl functional group (-OH) is bound to a carbon (1). The term alcohol originally referred to the primary alcohol ethanol (ethyl alcohol), which is used as a drug and is the main alcohol present in alcoholic beverages *(2).* Alcohol is absorbed from both stomach and small intestine, but is rapidly absorbed from the later (1). The rate of absorption varies; alcohol which gets distributed throughout the body water, heart tissues, brain and muscle are exposed to the same concentration as in blood. Ethyl alcohol absorption is very rapid when it is taken in empty stomach *(3).* The ethyl alcohol concentration in drink is between 20%- 30% depending on the type. The concentration of ethyl alcohol in liver is higher because it receives blood via the portal vein from stomach and small intestine. It is eliminated predominantly by hepatic metabolism and only 2-5% is excreted unchanged through urine and breath *(3).*

Alcohol consumption is a central feature of adult life in Nigeria and plays a major role in social, religious, political, and economic relationships (4) but should be discouraged due to some harmful effects on the health and social lives. Alcoholic beverages are consumed at virtually all ceremonies, including festivals, weddings, and funerals. Its consumption is a common practice in both rural and urban societies in Nigeria (4). Chronic alcohol consumption represents a major risk factor for the development of liver fibrosis, alcohol liver diseases (ALD), and hepatocellular carcinoma (HCC) *(5).* Alcohol causes dysfunction of almost all major organs including brain, liver, heart, pancreas, adrenal gland and thyroid gland *(2).* In 1990, the World Health Organization (WHO) estimated that globally alcohol accounts for 3.5% of the total days that are lost due to death and disability *(5).*

Prothrombin time (PT) is a measure of the integrity of the extrinsic pathways of the pro-coagulant cascade (6). The PT represents the time, in seconds, for patient plasma to clot after the addition of calcium and an activator of the extrinsic pathway (thromboplastin). Thus, deficiencies or inhibitors of clotting factors within the extrinsic pathways result in prolongation of the Prothrombin Time. Prothrombin Time is used to diagnose bleeding disorder (6). For patients taking blood-thinning medication e.g. warfarin, a regular PT tests help to ensure that they are not taking so much medication that make them susceptible to excessive bleeding. The test may also be used to check how the blood of people with liver disease or vitamin K deficiency clots. This is because these conditions can cause a bleeding disorder to develop (7).

The Activated Partial Thromboplastin Time (APTT) in contrast to the Prothrombin Time, measures the activity of the intrinsic and common pathways of the coagulation cascade (8). The division of the clotting cascade into the intrinsic, extrinsic and common pathways has little *in vivo* validity but remains a useful concept for interpreting the results of laboratory investigations (9). The APTT represents the time, in seconds, for patient plasma to clot after the addition of phospholipid, an intrinsic pathway activator, and calcium. APTT is a routine screening test for the investigation of bleeding tendency, in both acquired and congenital disorders (10). It is also indicated pre-operatively to detect a hypocoagulable state that can lead to excessive bleeding during or after surgery and in bleeding disorders (9).

Fibrinogen is a glycoprotein that in vertebrates circulates in the blood (11). During tissues and vascular injury, it is converted enzymatically by thrombin to fibrin and subsequently to a fibrin-based blood clot. Fibrinogen functions primarily to occlude blood vessels and thereby stop excessive bleeding (12). However, fibrinogen's product, fibrin, binds and reduces the activity of thrombin. This activity, sometimes referred to as antithrombin I, serves to limit blood clotting. Decreased fibrinogen concentration or impaired function can lead to haemorrhage (11). Thus fibrinogen testing is frequently utilized in the setting of trauma and surgery to determine the need for replacement product. In addition to trauma and surgery settings, fibrinogen concentration may also be reduced in consumptive coagulopathies, fibrinolytic therapy and due to compromised fibrinogen synthesis (13).

Alcohol consumption from many epidemiological studies has shown that it has some beneficial effect to the body system (14). Moderate alcohol consumption can reduce the risk of heart disease and ischemic stroke by 20 to 60% and death of all causes by 10 to 20% (15). The underlying factors contributing to the protective or pathophysiologic effects related to alcohol consumption are not well understood. Nevertheless, the adverse effect of alcohol if consumed in excess is dangerous. Alcohol is a drug that depresses the central nervous system like sedative and anesthetics (16). It is not a stimulant as widely believed but speech becomes free and social inhibition may be forgotten since it affects the portion of the brain that control judgment (16). It infiltrates the brain, liver, heart, pancrease, lung and kidney within minutes and passes into the blood stream (17). Haemostatic factors have been reported to be associated with coronary heart disease (CHD), morbidity and mortality in both men and women. Fibrinogen, factor VII, and von Willebrand (vWF) are coagulation factors that may increase the likelihood of thrombotic diseases, whereas plasminogen activator inhibitor-1 (PAI-1) is the rapid inhibitor of the endogenous fibrinolytic enzyme system. Fibrinogen may contribute to CHD by influencing the progression of coronary atherosclerosis as well as by precipitating the formation of occlusive thrombus (18). The association of alcohol consumption and coronary heart disease (CHD) is complex (14).

Materials and Methods

Study Area

The study was carried out in Old Airport Area, South Local Government Area, Sokoto, Nigeria. According to United Nations Fund for Population Activities (UNFPA) (19), Sokoto state lies in the (longitude 11^0-13^0-50^0 East and latitude 4-6^0 North), North- Western Nigeria. Sokoto state shares boundaries with the Republic of Niger to the North, Kebbi state to the West and South, and Zamfara state to the South and East. It occupies an area of short-grass savannah vegetation in the south and thorn scrub in the north. A generally arid region that gradually merges into the desert across the border in Niger republic. The state covers a total land area of about 25,973 square kilometers with a population of 3,702,676 and has a projected population 5,138,829 for year 2019 of according to 2006 census (20).

Subjects

The subjects used for this research were alcoholics and non-alcoholics in Old Airport Area, Sokoto South Local Government Area, Sokoto state.

Study Design
This was a cross-sectional study. The research work was conducted between June and November, 2019. Alcoholics of all age groups were recruited for this study. Prothrombin Time, Activated Partial Thromboplastin Time and Plasma Fibrinogen concentration was determined using the method by Barbara *et al.* (21) and Ingram (22) respectively. The samples were analysed in the department of Haematology, Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto.

Sample Size
Sample size was determined with G-power 3.0 software

Ethical Approval and Informed Consent
Ethical approval was obtained from the Ethics and Research Committee of the State ministry of Health, Sokoto (SKHREC/035/019).

Informed Consent
Written Informed consent was sought from each subject who participated in this study

Inclusion And Exclusion Criteria
Apparently healthy males and females alcoholic takers within the period of the study, not currently undergoing any medication and willing to give their consent were included in the study. While non-alcoholics individuals, currently undergoing medications and those who refused to give their consent were excluded from the study.

Sample Collection
Six millilitres (6.0ml) of venous blood were collected from the subjects of which 4.5mls was dispensed into 0.5ml of tri-sodium citrate anticoagulant container for the estimation of PT and APTT, and the other 1.5mls was dispensed into ethylenediaminetetra acetic acid (EDTA) container containing 0.02ml of anticoagulant for the plasma fibrinogen estimation and centrifuged at 3000rpm for ten minutes to obtain the plasma. The plasma was stored at -20ºC until required for analysis.

Laboratory Investigations
Prothrombin Time Test (21)

Procedure
Calcium rabbit brain thromboplastin (200µl) was placed in a clotting tube, within a water bath at 37^0c. It was incubated for 2 minutes. Then 100µl of plasma was added and the stop watch was started immediately. The tube was tilted gently at regular intervals and the time for the formation of clot was recorded. This is known as the Prothrombin time.
Normal range: 10 – 15 seconds (Agape)
PT Reagent: Agape Diagnostics reagents from Switzerland GmbH.

Activated Partial Thromboplastin Time (21)

Procedure

Kaolin platelet substitute mixture (200µl) was added in a clotting tube in a water bath at 37^0c. It was incubated for 2 minutes. Then 100µl of test plasma was added, and the tube was tilted gently at intervals for exactly 2 minutes. Then 100µl of 0.025M calcium chloride was added and the stop watch was started. The tube was tilted at regular intervals and the time of clot formation was recorded. The test was carried out in duplicate for both the control and the patient's sample and mean value for each obtained. This clotting time is called the Activated Partial Thromboplastin Time (APTT). APTT Reagent: Agape Diagnostics reagents from Switzerland GmbH

Plasma Fibrinogen Estimation (22)

Method: Modified clot-weight

Procedure

Firstly, 1ml of test plasma was pipetted into appropriately labelled test tube in water bath at 37^0C. Then 1ml of pre-warmed 0.025mol/L $CaCl_2$ was added to each tube and mixed. The mixtures were then incubated at 37^0C water bath with applicator stick dipped into each so that the fibrin clot was formed round the stick about 30mins later. When all adherent fibrin were removed from the water bath, it was washed in distilled water three times and then blot dry carefully with Whatman filter paper No 1. These were kept for 4days at room temperature to dry and then weighed.

Calculation:

Dry weight x 10g/100ml
= Volume of plasma

Fibrinogen = 200-400mg/dl (2-4g/L)

Statistical Analysis

Data were analysed using statistical package for social sciences (SPSS, version 20, Inc Chicago, USA) Software. All results were presented as mean ± standard deviation. Comparisons between the subjects and controls were done using student's t-test. The relationships between prothrombin Time, activated partial Thromboplastin Time and Plasma Fibrinogen concentration in relation to age group, gender and degree of alcohol consumption were tested using Spearman's correlation. A p-values <0.05 was considered significant.

Results

Table 1 shows the results of the PT, APTT and FC of the subjects and control. The results obtained showed that there was a significant increase ($p < 0.05$) in the prothrombin time (PT) and activated partial thromboplastin time (APTT) of the subjects compared with the control ($p < 0.05$). The mean PT and APTT of the subjects and control were (16.50±2.22 and 13.19±1.23 seconds) and (40.88±2.68 and 32.00±3.97 seconds) respectively. There was a significant decrease ($p<0.05$) in the plasma fibrinogen concentration (FC) of the subjects compared with the control ($P<0.001$). The FC of the subjects and control was 302.24±20.5 and 318.6±17.8 mg/dL respectively.

Table 1: Mean Distribution of PT, APTT and FC of the Subjects and Control

Parameters	Subjects (n=128)	Control (n=64)	t-value	*P*-value

PT (Seconds)	16.50±2.22	13.19±1.23	25.014	0.001
APTT (Seconds)	40.88±2.68	32.00±3.97	20.160	0.001
FC (mg/dL)	302.24±20.5	318.6±17.8	17.412	0.001

Key: **PT**: Prothrombin time; **APTT**: Activated Partial Thromboplastin Time; **FC** – Plasma Fibrinogen concentration, n=number
Significant difference = $p<0.05$

Table 2 shows the gender distribution of the PT, APTT and FC in the subjects studied. The results showed no significance difference in prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma fibrinogen concentration (FC) in male subjects compared with the female subjects studied ($p>0.05$). The mean PT and APTT of male and female subjects were (17.36±2.57 and 16.00±2.26 seconds) and (42.68±5.41 and 40.69±5.56 seconds), while the mean FC of the male and female subjects was 310.74±21.8 and 297.15±23.4 mg/dL respectively.

Table 2: Gender Distribution of the PT, APTT and FC in the Subjects

Parameters	**Males (n=98)**	**Females (n=30)**	**t-value**	***P*-value**
PT (Seconds)	17.36±2.57	16.00±2.26	-49.48	0.551
APTT (Seconds)	42.68±5.41	40.69±5.56	-60.09	0.625
FC (mg/dL)	310.74±21.8	297.15±23.4	-125.42	0.441

Key: **PT**: Prothrombin time; **APTT**: Activated Partial Thromboplastin Time; **FC:** Plasma Fibrinogen concentration, n= number
Significant difference = $p<0.05$

Table 3 shows the age distribution of the PT, APTT and FC in the subjects studied. The results obtained showed that there was a significant increase in the prothrombin time (PT) of the various age groups ($p<0.05$) while activated partial thromboplastin time (APTT) and plasma fibrinogen concentration (PFC) in subjects showed no significant increase in the various age groups ($p>0.05$). It also shows a positive correlation in the PT($r=0.263$), APTT($r=0.034$) and PFC($r=0.051$). The mean PT and APTT of the various subjects age groups were (15.75±1.74 and 40.85±2.88), (16.93±2.22 and 41.20±2.81), (17.82±2.64 and 40.91±2.34) and (15.75±1.25 and 41.25±0.96) Seconds while the mean FC of the various subjects age groups was (302.85±25.9), (305.60±18.3), (302.27±17.2) and (298.25±41.2) mg/dL respectively.

Table 3: Age Distribution of PT, APTT and FC in the Subjects

Age Range	**PT (Seconds)**	**APTT(Seconds)**	**FC(mg/dL)**

18 – 27	15.75±1.74	40.85±2.88	302.85±25.9
28 – 37	16.93±2.22	41.20±2.81	305.60±18.3
38 – 47	17.82±2.64	40.91±2.34	302.27±17.2
48 – 57	15.75±1.25	41.25±0.96	298.25±41.2
P-Value	0.033	0.408	0.362
r-Value	0.263	0.034	0.051

Key: **PT**: Prothrombin time; **APTT**: Activated Partial Thromboplastin Time; **FC:** Plasma Fibrinogen concentration, Significant difference = $p<0.05$

Table 4 shows the mean distribution of the PT, APTT and FC of the subjects according to the degree of alcohol consumption. The results showed no significant difference in the prothrombin time (PT) ($p <0.05$). And there was significant increase in Activated partial thromboplastin time (APTT) of heavy consumers compared to moderate consumers ($p <0.05$). Also, there was significant increase in the Fibrinogen concentration (FC) of the heavy consumers compared to moderate consumers ($p <0.05$). The mean PT and APTT of heavy consumers and moderate consumers were (17.93±2.33 and 15.94±2.69 seconds) and (43.42±5.94 and 36.18±2.63 seconds), while the mean plasma fibrinogen concentration was 316.82±19.4 and 277.19±22.2 mg/dL respectively for heavy and moderate consumers.

Table 4: Mean Distribution of PT, APTT and FC in the SUBJECTS According to the Degree of Alcohol Consumption

Parameters	Heavy (n=55)	Moderate (n=73)	t-value	*P*-value
PT (Seconds)	17.93±2.33	15.94±2.69	-49.04	0.087
APTT (Seconds)	43.42±5.94	36.18±2.63	-57.99	0.001
FC (mg/dL)	316.82±19.4	277.19±22.2	-126.87	0.002

Key: **PT**: Prothrombin time; **APTT**: Activated Partial Thromboplastin Time; **FC**: Plasma Fibrinogen concentration
Significant difference = $p<0.05$.

Discussion

Alcoholism has been a major menace and cause of morbidity and can lead to so many medical complications in Nigeria. Haemostatic disorders are directly involved in the atherosclerotic process. Prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma fibrinogen concentration (FC) are important clinical parameters for assessing extrinsic and intrinsic factors or pathways of the coagulation system (23). This study was carried out to

determine the haemostatic variables of alcoholics in Old Airport Sokoto state, Nigeria. The mean age of the subjects and control were 30±10.12 and 25±8.04 years respectively.

The results obtained showed that there was a significant increase in the prothrombin time (PT) and activated partial thromboplastin time (APTT) of the subjects compared with the control ($p<0.05$). There was also a significant decrease in the plasma fibrinogen concentration (FC) of the subjects compared with the control ($p<0.05$). Our finding in this present study is in consonance with previous reports which indicated that alcohol consumption increases haemostatic variables such as PT and APTT which can cause hypocellularity leading to anemia, leucopenia, thrombocytopenia and their relative squeal (1). Chronic alcoholism has been linked to insufficient availability of iron and other vital micronutrients such as vitamin B12 and folate for erythropoietic activities. This could be due to the inability of the ethanol irritated sticky intestinal mucosa to absorb these essential blood forming micronutrients which eventually result in impaired haemopoeisis (24, 25). This may be because excess intake of alcohol causes liver diseases and since most blood clotting factors are produced from the liver, there is high tendency that presence of alcohol in the system will affect the liver's normal function as such there will be deficiency of some clotting factors leading to prolongation PT, APTT and PFC.

In this study the genders distribution of the haemostatic parameters in the subjects studied showed no significance difference in prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma fibrinogen concentration (FC) in male subjects compared with the female subjects studied ($p>0.05$). This may be because only a few females participated in the research, The reason we had more male subjects (Alcoholics) participating in this research could be due to religious beliefs in the northern part of this country where women shy away from the fact that they consume alcohol so recruiting female alcoholics was more difficult as compared to males which are more easily accessible.

A significant positive correlation between age groups of alcoholics and increased PT and APTT was observed. The results also showed a significant increase in the PT ($p<0.05$) and a none significant increase in APTT ($p>0.05$) in various age groups. The results of this study are in agreement with results from previous studies (26, 27). From this study, the positive correlation between PT and age can be seen in the various age groups especially in (38- 47) where PT with the highest time was recorded, they could be because most of the alcoholics in this age group were family men and women who had various family issues and as such tend to drink more of alcohol as they tend to find comfort in alcohol consumption.

The results also showed a significant increase in the PT and APTT in heavy consumers compared with moderate consumers ($p<0.05$). The results of this study are in agreement with results from previous studies (1, 28) which showed significant evidence that links alcoholism to increased levels of PT and APTT. The report of the study carried out by Tripodi and Mannucci, indicates that consumption of commonly ingested quantities of alcohol correlated with the development of a hypocoagulable state in men (28). The effect of alcohol consumption was more pronounced in the heavy drinkers than the moderate drinkers. Dimmitt *et al.* (1) reported that this effect might be due to the toxic effect on the bone marrow, where the platelets and other blood cells are been produced. This is dangerous for the alcoholics. This may be because the alcoholics used were mostly consuming alcohol and no other intoxicating drugs like syrup such as codeine and tutolin.

In this study, the fibrinogen concentration was significantly lower in the subjects compared with the control ($p<0.05$). Similarly, the fibrinogen concentration was also significantly lower in heavy

consumers compared with moderate consumers. The result of this study is in agreement with previous studies (29, 27, 30) which reported that alcohol consumption decreases plasma fibrinogen concentration, reduce whole-blood and plasma viscosity *in vivo*, increase erythrocyte deformability *in vitro*, as well as favourably affect the serum lipid profile *in vivo*. According to Hendriks et al., (30), if fibrinogen is a causal risk factor for cardiovascular diseases, it may be one of the variables that explain the protective effect of moderate alcohol consumption on cardiovascular diseases. This may be due to the fact that most of the alcoholic recruited for the study were healthy and none of them have had any previous organ transplant in the past such as Liver or kidney transplant.

Conclusion

In conclusion, the PT and APTT is significantly increased while plasma fibrinogen concentration significantly decreased in in alcoholics compared to non-alcoholics. However, the variation of these parameters in subjects with respect to gender did not show any significant difference, but showed significant difference with respect to degree of consumption. The study concludes that rate of consumption of alcohol has effect on PT, PTTK and PFC. Prothrombin Time, Activated Partial Thromboplastin Time and Plasma Fibrinogen Concentration should be included in routine test to monitor patients with alcohol related disorders. There is need to enact laws that regulate the production, sales and consumption of various alcoholic beverages to prevent abuse and protect the health of citizens. Further studies should be carried out on the effect of alcohol consumption on other haemostatic parameters not covered in this study and in other area and with larger sample size.

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