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Evaluation of Coagulation Factors Seven (FV11) And Twelve (FX11) in Post Intensive Phase of Tuberculosis Disease Treatment in Bayelsa State, Nigeria

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Abstract: Tuberculosis, a major health concern and leading infectious disease in man. It is caused by Mycobacterium tuberculosis. Research shows that Tuberculosis affects the coagulation factors and causes elongated Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in infected subjects. This research was conducted to evaluate coagulation factor VII and XII, in TB disease and treatment. Three facilities in Bayelsa State were used. Fifty newly diagnosed Tuberculosis subjects and fifty apparently healthy controls were studied. Tuberculosis subjects were monitored at two months interval of treatment till the sixth month. Sputum was used for assay of Tuberculosis using Ziehl-Neelsen Technique and the GeneXpert and plasma for PT and APTT assay. FVII and FXII were analysed using OPSY-MR Enzyme Linked Immunosorbent Assay machine using reagents from Glory Science Inc. (China). Statistical product for service solution (SPSS) software version 25 was employed in the data analysis. A p - value of <0.05 was considered significant. Results shows significantly higher PT and APTT values but significantly lower FVII value in newly diagnosed Tuberculosis subjects compared to control group. There was no significant difference in FXII ($p>0.05$) in new Tuberculosis subjects compared to controls. These results indicates that Tuberculosis disease altered all the parameters studied except coagulation factor XII. However, all altered parameters returned to almost control values at the end of the fourth month of treatment. We conclude from this study that the reduced values of FVII contributes to the elongation of PT in Tuberculosis patients while FXII is not altered and so does not contribute to the elongated APTT in Tuberculosis patients.

Keywords, Coagulation Factor VII, Coagulation Factor XII, Haemostasis, Tuberculosis

Introduction

Tuberculosis disease also known by the acronym TB, is caused usually by *Mycobacterium tuberculosis* (MTB) bacteria. It is primarily a disease of the lungs, although other parts of the body can be affected (WHO, 2020a). In recent years, Nigeria was having the highest disease burden in Africa (Federal Ministry of Health.,2019, Ibrahim *et al*, 2022, Okpokoro *et a*l, 2023).

Coagulation, which is also called clotting, is a process in which blood changes from a liquid form into a gel, resulting to a blood clot. This process leads to haemostasis, the stoppage of blood loss from a injured vessel and closely followed by repair. The mechanism of coagulation involves activation, adhesion and aggregation of platelets, as well as deposition and maturation of fibrin (Keragala *et al*. 2018).

The process of Coagulation begins almost immediately following a damage to the endothelium lining a blood vessel. The exposure of blood to the subendothelial space activates two processes: changes in platelets and the exposure of subendothelial tissue factor to plasma factor VII, which ultimately leads to cross-linked fibrin formation. Platelets immediately form a plug at the site of injury; this is called primary

haemostasis. Secondary haemostasis follows at the same time: additional coagulation (clotting) factors aside factor VII reacts in a cascade to form fibrin strands, which fortifies the the platelet plug (Keragala *et al*. 2018).

The series of coagulation cascade of secondary haemostasis has two initial pathways which lead to fibrin formation. These are a series of reactions, in which an inactive enzyme precursor known as a Zymogen of a serine protease and its glycoprotein co-factor are activated and becomes active components that thereafter catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin. Coagulation factors are indicated by Roman numerals, with a lowercase *a* attach to indicate an active form. These are the contact activation pathway (also known as the intrinsic pathway), and the tissue factor pathway (also known as the extrinsic pathway), which both lead to the same fundamental reactions that produce fibrin. It was previously thought that the two pathways of coagulation cascade were of equal importance, but it is now known that the primary pathway for the initiation of blood coagulation is the tissue factor (extrinsic) pathway (Pallister and Watson, 2010).

Disorders of coagulation are disease states which can result in problems with haemorrhage, bruising, or thrombosis (Turdikulovna *et a*l., 2023). Many research articles allude to the fact of the derangement in the secondary coagulation system as seen in the elongation of the Prothrombin Time Test (PT) and the Activated Partial Thromboplastin Time Test (APTT) in Tuberculosis patients (Saidu *et al*. 2019, Atiegha *et al.* 2022a, Atiegha *et al.* 2022b, Ulugbekovich and Haydarovich, 2023). It was therefore necessary for us to monitor these two coagulation factors (FVII and FXII) to know their values during Tuberculosis treatment knowing the important rule they play in secondary Haemostasis.

Material and method

Study area; The study area involved three locations; (1) The Tuberculosis and Leprosy Hospital Igbogene; (2) The Federal Medical Center (FMCY) and (3) Niger Delta University Teaching Hospital (NDUTH) all in Yenagoa Local Govt Area of Bayelsa state, Nigeria.

Study population: The population of the study was positive Tuberculosis patients attending the DOTS treatment center Igbogene, FMCY and NDUTH, Yenagoa, Bayelsa State Nigeria. They are comprised of Group 1. Apparently healthy (controls) age and gender- matched who meet the inclusion criteria. Group 2 were newly diagnosed Tuberculosis subjects who also meet the inclusion criteria. Group 3 were those progressing to DOTS first line regimen (2 months). Group 4 were those progressing to DOTS second line regimen (4 months) while Group 5 were those progressing to final treatment (6 months). All gender and ages were considered.

Test Methodology

Sample collection; Sputum was collected in a sterile wide mouthed container. Five (5ml) of blood was also collected by venous puncture and emptied into a serum separator tube. The tube was later centrifuged, and the serum separated into another plane container.

Sputum analysis; Sputum analysis was by the Ziehl-Neelsen Acid Fast Bacilli (AFB) technique as described by Sharma and Nagmoti (2021 and the GeneXpert technique by David Alan and Cepheid Inc. as modified by Catharina *et. al.* (2010) .

Principle of Ziehl-Neelsen (AFB) technique: TB bacilli when stained picks up the primary stain and appears red under the microscope.

Principle of the GeneXpert: The Gene Xpert MTB/RIF assay is a nucleic acid amplification (NAA) test that uses a disposable cartridge with the GeneXpert Instrument System.

Prothrombin Time (PT); The one stage prothrombin time method was be used as described by Dorgalaleh, *et al.* (2021). Principe of Prothrombin Time (PT) assay: When tissue thromboplastin and calcium ions are added to plasma, the extrinsic clotting factors are activated. This results to the generation of Thrombin and the formation of fibrin clot.

APTT; Principle of APTT test: The capacity of blood to form a fibrin clot by way of the intrinsic haemostatic pathway requires coagulation factors 1, 11, V, V111, IX, X, X1 and X11,

platelet lipids and calcium. The assay is performed by the addition of a suspension of rabbit brain cephalin with surface activities (Lardinois, *et al.,* 2022). This test measures deficiency of coagulation factors in the intrinsic and the final common pathway.

FVII and FXII: The tests were done using the kits from Glory Science (G Science Co. Ltd, China). Principle of test: The Gscience ELISA (Enzyme-Linked Immunosorbent Assay) kit is an in vitro ELISA for the quantitative measurement of F VII and F XII in Serum/Plasma. This assay employs an antibody specific for each parameter coated on a 96-well plate. The stop solution changes the colour from blue to yellow and the intensity of the colour is measured at 450nm using a spectrophotometer.

Result

Table 1. is the ANOVA for Haemostatic variables in Group 2, Group 3, Group 4 and Group 5. There was a significant progressive decrease in the mean value of PT (p = 0.000) from 14.12±1.85s in Group 2 subjects to 13.36±1.83s in Group 3 subjects to 11.87± 1.85s in Group 4 subjects to 11.48±1.65s in Group 5 subjects TB subjects when compared. The values of APTT were also significantly decreased (p = 0.000) from Group 2 to Group 5 subjects. The table further reveals that there was a significant progressive increase (p = 0.000) in the values of FVII when Group 2 (6.51±1.02), Group 3 (8.50 ± 2.10), Group 4 (8.63 ±2.10ngmll) and Group 5 subjects were compared. There was no significant deference (p=0.132) when the values of FXII were compared.

Table 1; ANOVA for Haemostatic variables in Groups 2, 3, 4 and 5 subjects

Parameter	**Variable**	Group 2	Group 3	Grroup 4	Group 5	F value	P value
	N=	**50**	**46**	**41**	**39**		
PT(sec)	Mean±SD	14.12±1.85	13.36±1.83	11.87± 1.85	11.48±1.65	23.114	0.000
APTT (sec)	Mean±SD	32.84±4.94	29.65±4.79	26.75±3.47	26.26±4.05	21.522	0.000
F. XII (ng/ml)	Mean±SD	6.63±1.59	6.24±1.28	6.04 ±1.19	6.05±1.23	1.896	0.132
F. VII(ng/ml)	Mean±SD	6.51±1.02	8.50±2.10	8.63 2.13	8.74±2.12	15.321	0.000

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. FVII; coagulation factor VII. FXII; Coagulation factor XII. Group 2; Newly diagnosed TB subjects; Group 3; 1st Treatment TB subject; Group 4; 2nd Treatment TB subjects l Group 5; 3rd Treatment TB subjects

Table 2a. is the Post-Hoc for Haemostatic variables in Group 1, Group 2 and Group 3 subjects. There were significant differences (p = 0.000) when Group l values of PT, APTT, and F VII were compared to values of Group 2 subjects. There was no significant difference (p = 0.338) when Group 1 values of F XII was compared to values of Group 2 subjects.

There were significantly higher mean values (P= 0.000) of PT and APTT when Group 1 (11.66±1.34s and 26.54±3.45s) were compared with Group 3 (13.36±1.83s and 29.65±4.79s). There were no significant differences (p>0.05) in the mean values of Factor XII and FVII when Group1 values of 6.19±1.49s and 8.95±3.20s were compared to Group 3 values of 6.24 ±1.28s and 8.50±2.10s.

Table 2a; Post-Hoc for Haemostatic variables in Groups 1, 2 and 3 subjects .

Parameter		Group 1	Group 2	p-value	Group 1	Group 3	P value
	N	**50**	**50**		**50**	**46**	
PT(sec)	Mean±SD	11.66±1.34	14.12±1.85	0.000	11.66±1.34	13.36±1.83	0.000
APTT (sec)	Mean±SD	26.54±3.45	32.84±4.94	0.000	26.54±3.45	29.65±4.79	0.000
F. XII (ng/ml)	Mean±SD	6.20±1.49	6.63±1.59	0.388	6.19±1.49	6.24 ±1.28	0.867
F. VII(ng/ml)	Mean±SD	8.95±3.20	6.51±1.02	0.000	8.95±3.20	8.50±2.10	0.431

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. F VII; coagulation factor VII. F XII; Coagulation factor XII. Group 1, Control group; Group 2; Newly diagnosed TB subjects; Group 3; 1st Treatment TB subject

Table 2b.; is the Post-Hoc for Haemostatic variables in Group 1, Group 4 and Group 5 subjects. There were no significant difference ($p>0.05$) when control values of all parameters in Group 1 were compared to the Group 4 subjects. It was 11.66±1.85 and 11.87±1.85 for Group 1 and Group 4 subjects respectively for PT ($p = 0.461$). Others are 26.54±3.45/26.75±3.47, ($p=0.768$) for APTT. For It is 6.19±1.48/6.04 ±1.19ng/ml ($p=0.605$) for FXII while that of FVII is 8.95±3.20/8.63 2.13 and a p value of $p=0.590$. Lastly, the table shows There were no significance difference ($p > 0.05$) when values of Group 1 were compared with Group 5 subjects in all haemostatic parameters.

Table 2b; Post-Hoc for Haemostatic variables in Groups 1, 4 and 5 subjects.

Parameter		Group 1	Group 4	p-value	Group 1	Group 5	P value
	N	**50**	**41**		**50**	**39**	
PT(sec)	Mean±SD	11.66±1.34	11.87± 1.85	0.461	11.66±1.34	11.48±1.65	0.590
APTT (sec)	Mean±SD	26.54±3.45	26.75±3.47	0.768	26.54±3.45	26.26±4.05	0.723
F. XII (ng/ml)	Mean±SD	6.20±1.49	6.04 ±1.19	0.605	6.20±1.49	6.05±1.23	0.267
F. VII(ng/ml)	Mean±SD	8.95±3.20	8.63 2.13	0.590	8.95±3.20	8.74±2.12	0.733

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. F VII; coagulation factor VII. F XII; Coagulation factor XII. Group 1, Control group; Group 4; 2nd Treatment TB subjects l Group 5; 3rd Treatment TB subjects

Table 2c shows the Post-Hoc for Haemostatic variables in Groups 2, 3 and 4 subjects. There were significant decreases in the values of PT and APTT, leading to p-values of 0.049 and 0.002 respectively in Group 2 compared to Group 3 subjects. There was significant increase ($p = 0.000$) in the value of FVII when Group 2 subjects were compared to Group 3 subjects. There was no significant difference in the values of FXII ($P= 0.101$) in Group 2 subjects when compared to Group 3 subjects.

There were significant decrease in the values of PT and APTT ($p= 0.000$ and 0.000 respectively) in Group 2 subjects when compared to Group 4 subjects. There was significant increase ($p = 0.000$) in the value of FVII when Group 2 subjects were compared to Group 4 subjects. There was no significant difference in the values of FXII ($P= 0.056$) in Group 2 subjects when compared to Group 4 subjects.

Table 2c; Post-Hoc for Haemostatic variables in Groups 2, 3 and 4 subjects

Parameter		Group 2	Group 3	p-value	Group 2	Group 4	P value
	N	**50**	**46**		**50**	**41**	
PT(sec)	Mean±SD	14.12±1.85	13.36±1.83	0.049	14.12±1.85	11.87± 1.85	0.000
APTT (sec)	Mean±SD	32.84±4.94	29.65±4.79	0.002	32.84±4.94	26.75±3.47	0.000
F. XII (ng/ml)	Mean±SD	6.63±1.59	6.24 ±1.28	0.197	6.63±1.59	6.04 ±1.19	0.056
F. VII(ng/ml)	Mean±SD	6.51±1.02	8.50±2.10	0.000	6.51±1.02	8.63 2.13	0.000
D-D. (ng/ml)	Mean±SD	418.10±111.7	379.0±119.6	0.101	418.10±111.7	212.90 ±78.5	0.000

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. F VII; coagulation factor VII. F XII; Coagulation factor XII. Group 2; Newly diagnosed TB subjects; Group 3; 1st Treatment TB subject; Group 4; 2nd Treatment TB subjects

Table 2d; is the Post-Hoc for Haemostatic variables in Groups 2, 3, 4 and 5 subjects. There were significant decreases in the values of PT (14.12±1.85s and 11.48±1.65s, p=0.000), APTT (32.84±4.94s and 26.26±4.05s, p=0.000), when Group 2 subjects were compared with Group 5 Subjects. F VII increased significantly from 6.51±1.02 to 8.74±2.12 with a p value p=0.000. There was no significant difference (p>0.05) in the value of F XII when Group 2 subjects were compared with Group 5 Subjects.

There were significant decreases in the values of PT and APTT (P= 0.000 and 0.020, respectively) in Group 3 subjects were compared with Group 4 Subjects. There was no significant difference in the values of FXII (p= 0.463) and FVII (p = 0.783) in Group 3 subjects were compared with Group 4 Subjects.

Table 2d; Post-Hoc for Haemostatic variables in Groups 2, 3, 4 and 5 subjects.

Parameter		Group 2	Group 5	p-value	Group 3	Group 4	P value
	N	**50**	**39**		**46**	**41**	
PT(sec)	Mean±SD	11.66±1.34	11.48±1.65	0.000	13.36±1.83	11.87± 1.85	0.000
APTT (sec)	Mean±SD	26.54±3.45	26.26±4.05	0.000	29.65±4.79	26.75±3.47	0.002
F.XII (ng/ml)	Mean±SD	6.20±1.49	6.05±1.23	0.066	6.24 ±1.28	6.04 ±1.19	0.463
F. VII(ng/ml)	Mean±SD	8.95±3.20	8.74±2.12	0.000	8.50±2.10	8.63 2.13	0.783

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. F VII; coagulation factor VII. F XII; Coagulation factor XII. Group 2; Newly diagnosed TB subjects; Group 3; 1st Treatment TB subject; Group 4; 2nd Treatment TB subjects l Group 5; 3rd Treatment TB subjects.

Table 2e is the Post-Hoc for Haemostatic variables in Group 3, 4 and 5 subjects. There were significantly reduced (p>0.05) values of PT and APTT when Group 3 subjects were compared with Group 5 Subjects. There was no significant difference (p>0.05) in the value of F XII and F VII when Group 3 subjects were compared with Group 5 Subjects .Lastly, there was no significant difference (p>0.05) in the value of all haemostatic parameters when Group 4 subjects were compared with Group 5 Subjects.

Table 2e: Post-Hoc for Haemostatic variables in Group 3, 4 and 5 subjects.

Parameter		Group 3	Group 5	p-value	Group 4	Group 5	p-value
	N	46	39		41	39	
PT(sec)	Mean±SD	13.36±1.83	11.48±1.65	0.000	11.87± 1.85	11.48±1.65	0.261
APTT (sec)	Mean±SD	29.65±4.79	26.26±4.05	0.001	26.75±3.47	26.26±4.05	0.555
F.XII (ng/ml)	Mean±SD	6.24 ±1.28	6.05±1.23	0.487	6.04 ±1.19	6.05±1.23	0.965
F. VII(ng/ml)	Mean±SD	8.50±2.10	8.74±2.12	0.607	8.63 2.13	8.74±2.12	0.815

Key: PT; Prothrombin Time Test. APTT; Activated Partial Thromboplastin Time Test. F VII; coagulation factor VII. F XII; Coagulation factor XII. Group 3; 1st Treatment TB subject; Group 4; 2nd Treatment TB subjects l Group 5; 3rd Treatment TB subjects

Discussions

In this current study, the results showed a significantly higher PT (14.12±1.85 seconds) vs (11.66±1.34 seconds), p=0.000); APTT (32.84±4.94 seconds vs 26.54±3.45 seconds), p=0.000) and a significantly lower FVII (6.51±1.02ng/ml vs 8.95±3.20ng/ml), p=0.000) values in newly diagnosed Tuberculosis subjects compared to control group. FXII showed no significant difference (6.20±1.49ng/ml vs 6.63±1.59ng/ml), p>0.05) in new Tuberculosis subjects compared to controls. These results shows that Tuberculosis disease altered all the parameters studied except coagulation factor XII. Similar outcomes were obtained by some researchers (Suryakusumah *et al*. 2021, Okoroiwu, *et al*. 2022, *Oloro, et al.* 2022).

This study further focuses on the values of parameters under consideration in the post-intensive phase of tuberculosis treatment. The tables above considered the values of haemostatic parameters during the end of the first phase (two months) of anti-TB therapy here known as the 1st treatment group (Group 3) and the end of the fourth (4th) month period of treatment here known as 2nd treatment group (Group 4) as well as the end of the 6th month here known as the 3rd treatment group (Group 5).

All parameters (PT, APTT and FVII) were all tending towards control values. Those that were higher in values at the Newly diagnosed stage (PT, APTT) now have reduced values while FVII whose value was lower had started assuming higher value at the end of the 1st treatment phase. Again, it can also be said here that all factor responsible for the alterations of these values were not permanent and were being reversed during the treatment. Most of these parameters had their origin from the Liver. Hence it could be said that the liver of these study subjects was not permanently altered as regards their low level of production of these enzymes in the diseased state.

Coagulation factor VII (also known as proconvertin) was improved from 6.51±1.02ng/ml **at** the diseased state to 8.63 2.10ng/ml at the end of the fourth month of treatment. Here it is seen that the disease greatly impacted negatively on its level but the Anti-tuberculosis Therapy (ATT) was effective. Comparison of the values for controls and 2nd treatment group was not significant (p>0.05). There are few recorded diseases that adversely affects the value of coagulation factor F VII. Marcos-Contreras *et. al.* (2016) and Marcos-Contreras *et al*. (2016) noted that Factor VII deficiency is rare and inherited recessively. Guglielmo and Francesco (2009) also opined that the condition of factor VII deficiency may be

inherited or acquired and that it is the commonest of all the rare congenital coagulation disorders.

Symptoms of this disorder varies greatly. Some affected persons show few or no symptoms at all. On the other hand, others might experience life-threatening bleeding. Notably this bleeding anomaly presents itself as a tendency to easy bruising, nose bleeding, heavy and extended menstruation periods, and excessive bleeding after dental or surgical interventions (Girolami *et al.* 2017, Trillo *et al* 2022, Martinez- Garcia *et al*. 2023). From our study, the deficiency of coagulation factor VII in Tuberculosis disease is believed to produce mild symptom. It is known that about 3-4% of patients with FVII deficiency might also have thrombotic episodes(Yazicioglu *et al*., 2013; Iwaniec *et al.,* 2019).

In the acquired aspect of FVII deficiency, an insufficient amount of factor VII is said to be produced in the liver due to liver disease, vitamin K deficiency, or certain medications, e.g. Coumadin (WHO, 2017, Abdul Kadir and Gomez, 2022). In our study the anti -TB drugs did not affect the processes of factor VII production as seen in the elevated rate of the enzyme as treatment progresses.

Coagulation factor XII, also known as Hageman factor, is the second coagulation factor considered in this study. In all comparisons from control to Newly diagnosed to 1st, 2nd treatment and 3rd TB subjects, none was significant ($p>0.05$). Factor XII deficiency is noted to be a rare disorder that is inherited in an autosomal recessive manner. Unlike other clotting factors, it is noted that deficiencies in factor XII is totally asymptomatic and does not cause excess bleeding (Simão and Feener, 2017; Bachler *et al*., 2019). It is also known that in a mice experiment on FXII that mice lacking the gene for factor XII, are less susceptible to thrombosis (*Renné et. al., 2005)*. This current study demonstrates the fact that coagulation factor XII is not diminished in tuberculosis disease and so does not contribute to the prolonged PT/APTT in tuberculosis patients.

Another significant finding in this study are the insignificant values ($p<0.05$) of the comparison of the values of controls and 3rd treatment groups , as well as 2rd treatment and 3th treatment groups. At the treatment from the fourth to the sixth month there was an insignificant change in the value of the parameters under study.

Conclusion and recommendations

From the study carried out we have discovered that diminished value of coagulation factor VII also contributes to the morbidity of tuberculosis disease patients. Therefore, correction of coagulation factor VII should be incorporated into the treatment of TB. Also, all parameters studied reverted back to almost control values at the end of the fourth month of treatment. Therefore, there is the need for further studies to ascertain the possibility of making TB (DOTS) treatment to last for four months instead of six months.

Conflict of interest declarations.

There are no conflicts of interest in this Research work

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