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Some coagulation profile among patients with renal failure in Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria

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Abstract
Background: Renal failure or kidney failure is a condition in which the kidneys fail to adequately filter toxins and waste products from the blood. The World Health and Global Burden of Disease project reports show that kidney disease contribute to the global burden of diseases—with approximately 850,000 deaths every year and 15,010,167 disability-adjusted life styles. This study was carried out to estimate the Prothrombin Time (PT) and Partial Thromboplastin Time with Kaolin (PTTK) in kidney failure patients. Fifty (50) clinically confirmed renal failure patients serving as the tests group and fifty age- matched non-renal failure subjects served as control for the study. During the study, 4.5ml of blood was collected from the subjects (tests and controls) into a bottle containing 0.5ml of trisodium Citrate and analysed for Prothrombin Time (PT) and Partial Thromboplastin Time with Kaolin (PTTK). The PT and PTTK were determined using manual method according to the manufacturer's instructions. From the study, we observed that the mean PTTK and PT values of kidney failure patient and control groups were 33.7 ± 8.0 and 17.70 ± 3.9 seconds; and 36.3 ± 3.5 and 15.7 ± 1.6 respectively. The PTTK of tests subjects was lower and the PT was higher than that of controls ($p < 0.05$). The Mean ± standard deviation of PT of subjects males and females was compared with control males and females and found to be 16.3 ± 2.3 and 17.1 ± 3.8; 15.4 ± 1.1; and 16.0 ± 1.9 respectively. The PTTK was compared among subjects and control based on gender. The mean PTTK results were 35.0 ± 6.2 and 35.0 ± 6.4 for male and female subjects compared to 37.0 ± 3.9 and 35.8 ± 1.3 respectively for male and female controls. The difference however was not statistically significant ($p> 0.05$). We conclude that kidney failure leads to an increased in Prothrombin Time (PT) and decrease in Partial Thromboplastin Time with Kaolin (PTTK). These abnormalities in PT and PTTK could contribute to the bleeding diathesis found in patients with kidney failure. We advocate

that renal failure patients should be placed on a balanced diet to keep their vitamin K intake consistent from day to day. And any changes in their diet or use of supplements should be made known to their healthcare provider. Regular monitoring of the coagulation profile of patients with renal failure is recommended.

1. Introduction

Renal failure or kidney failure (formerly called renal insufficiency) is a condition in which the kidneys fail to adequately filter toxins and waste products from the blood. Acute kidney failure (ARF) or injury and chronic kidney disease (CKD) together with a number of other diseases may cause either form of renal failure. Whereas the incidence of ARF depends on the factors upon which it is defined, the incidence of advanced ARF (serum creatinine > 500 µmol/L) is about 70–140 per million of the population and around half of these will require dialysis[1]. The World Health Report 2002 and Global Burden of Disease project reports show that kidney disease contribute to the global burden of diseases—with approximately 850,000 deaths every year and 15,010,167 disability-adjusted life years. Globally, it represents the 12th cause of death and 17th cause of disability[2]. In the United State of America and Taiwan, the prevalence of CKD is put at about 12-13% despite the fact that most of these people may not be aware of their condition[3]. In Ghana, the prevalence of CKD varies from 4% to 46.9% depending on the population upon which it is determined[4.5.6]. In Nigeria, 27million people had CKD as of 2011, with the prevalence of 15,000 new cases occurring every year and 45,000 persons living with kidney failure annually according to the National kidney foundation.

Platelet or coagulation cascade disorder can lead to bleeding, while platelet hyper reactivity and abnormalities in the regulatory mechanisms may result in excessive thrombin formation and pathological thrombosis. Thrombotic complications and bleeding diathesis are some of the risks posed by renal disorder which in turn is associated with a high morbidity. Laboratory tests such as PT and PTTK are useful for assessing the etiology of kidney failure as well as establishing the level of injury/insult thereby helping in the proper management and prompt treatment of the patient.[7, 8]

There is a continuous increase in the prevalence of renal disease worldwide as well as in Nigeria. All subjects with the clinical syndrome of severe renal failure are at risk of bleeding diathesis. This predisposition becomes especially problematic when these patients undergo invasive procedures such as surgery, biopsy, or catheter placement. About 3-15% of the mortality rate among kidney disease of any etiology is linked with haemorrhagic propensity[9, 10]. Available information indicates that coagulation abnormalities are a consequence of uremia, renal artery damage, Von Willebrand factor, factor VIII and beta-thromboglobin activation. Other mechanisms may come into play leading to coagulopathy. These include Thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome and disseminated intravascular coagulopathy [11, 12]. In these bleeding abnormalities, changes in haemostatic parameters such as PT and PTTK, are extremely important determinants of morbidity and mortality[13, 14].

As the prevalence of renal disease varies in different communities with possible effect of diet, genetic make-up and other medical conditions. There is paucity of information on coagulation profile of kidney failure patients in Sokoto, North Western region of Nigeria. The aim of this study was to assess the impact of renal disease on the PT and PTTK.

1.1. Study Area

The study area was the Usmanu Danfodiyo Teaching Hospital Sokoto (UDUTH) established in the year 1975 in Sokoto metropolis. It is committed to the provision of tertiary health care services to the entire North-Western region and our neighboring border country - Niger Republic. The metropolitan city of Sokoto lies between longitude 11º 30" to 13º 50" east and latitude 4º to 6º north and covers an area of 28,232.37sq kilometer. It is bordered in the North by Niger Republic, in the East by Zamfara State and Kebbi State to the South and West[15]. Sokoto is one of the hottest cities in the world with an annual average temperature of 28.3C. The warmest months are February to April (temperatures exceed 45^0C) while the rainy season lasts from June to October and Harmmattan season starts from late October to February. There are two main seasons in Sokoto, the wet (October to April) and dry (May to September) [16]. The main occupation of the people is grain production and animal husbandry. More than 80 percent of its indigenes practice agriculture[17]. Crops produced include millet, beans, onions, tomatoes, rice, maize, guinea corn, wheat and cotton. Other occupations commonly practiced are dying, blacksmithing, weaving, carving, trading and cobbling. Sokoto ranks second in livestock production in Nigeria.

Sokoto state has a population of 4.5million[18], made up of Hausa and Fulani majority and a minority of Zabarmawa and Tuareg. The major language in this state is Hausa and Fulfulde among the Fulani. They have two major festivals Eid – el – fitri and Eid-el-kabir[15]. Socio cultural characteristics is homogenous as majority of its indigenes are Muslims, therefore the Muslim religion provides them the code of conduct and behavioural characteristics. Common practices are child marriage, polygamy, consanguity, multiple births, and male dominance.

1.2. Study Design

This study is a case – control study involving fifty (50) clinically confirmed renal failure patients (subjects) and fifty age- matched non-renal failure subjects (controls).

1.3. Inclusion Criteria

Presence of renal failure irrespective of whether acute or chronic as defined by the following criteria: persistent level

of serum creatinine greater than 1.2mg/dl and diagnosis of Acute or Chronic Renal Failure by other clinical criteria as determined by the managing clinicians.

1.4. Exclusion Criteria

Patients with congenital coagulation disorders and patients on anticoagulant therapy were excluded from the study.

2. Method

One hundred subjects were recruited for this study. Fifty of these subjects were confirmed patients with renal failure receiving care in Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto, while the remaining fifty subjects were normal healthy volunteers and serving as the control group. 4.5ml of blood was collected from both the renal failure patients (tests) and control by clean venipuncture and delivered into plastic tube containing 0.5ml trisodium citrate (16g/l). The anticoagulated blood was centrifuged at 1200g-2000g for 15 minutes and the platelet poor plasma was removed and placed in plastic tube and used for PT and PTTK test according to the manufacturer's instruction.

2.1. Ethical Approval

Ethical approval was obtained from the Hospital Ethical Committee and verbal informed consent was obtained from all the subjects before sample collection.

2.2. Statistical Data Analysis

Data collected was analysed using SPSS version 17 computer statistical software package. The results were expressed as mean ± SD. The paired t-test was used to determine significant difference between test and control subjects. Statistical significance level was put at $p \leq 0.05$.

3. Result

Table 1. *Mean values of Partial Thromboplastin Time with Kaolin (PTTK) and Prothrombin Time (PT) among controls and renal failure subjects*

Group	N	PTTK (Seconds)	PT(Seconds)
Controls	50	36.3±3.5	15.7±1.6
Subjects	50	33.7±8.0	17.7±3.9
p-value		0.037	0.001

Table 2. *Mean values of PT of subjects and controls based on gender*

Gender	Subjects	Controls
Males	16.3±2.3	15.4±1.1
Females	17.1±3.8	16.0±1.9
p-value	0.545	0.077

Table 3. *Mean values of PTTK of subjects and controls based on gender.*

Gender	Subjects	Controls
Males	35.0±6.2	37.0±3.9
Females	35.0±6.4	35.8±1.3
p-value	0.742	0.096

The mean PTTK and PT values of kidney failure patient and control groups were 33.7 ± 8.0 and 17.70 ± 3.9 seconds and 36.3 ± 3.5 and 15.7 ± 1.6 respectively. We found that there were statistically significant difference between PTTK and PT values of kidney failure patients and controls ($p < 0.05$) as shown in table 1. In table 2, the Mean ± standard Deviation of PT of subjects males and females was compared with control males and females (16.3 ± 2.3 and 17.1 ± 3.8; 15.4 ± 1.1 versus 15.4± 1.116.0 ± 1.9 respectively). Similarly, the PTTK was compared among the subject and control based on gender (35.0 ± 6.2 and 35.0 ± 6.4 versus 37.0 ± 3.9 and 35.8 ± 1.3 respectively) and was found to have no significant difference in PT and PTTK ($p > 0.05$) across the gender.

4. Discussion

In this present study, we observed that the mean PTTK and PT values of kidney failure patient and control groups were 33.7 ± 8.0 and 17.70 ± 3.9 seconds and 36.3 ± 3.5 and 15.7 ± 1.6 respectively. There was a statistically significant difference between PTTK and PT values of kidney failure patients and controls ($p < 0.05$) as shown in table 1. The mean PT value from our work was 2 seconds higher in patients with renal failure than the individual without renal failure. This is in agreement with the work of Rafig and coworkers [19] who found out that the PT value in ninety patients with Acute Renal Failure was significantly higher than the control group. Our finding is also consistence with previous report among renal failure patients before dialysis[19, 20]. However, our work is at variance with the work of Misra and colleagues and also that of Anand and coworkers both of whom observed no statistical significant differences[21, 22].

The increase in PT (which is used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status and in the identification of the anticoagulants dicumarol and warfarin, and was used subsequently as a measure of activity for warfarin. When used therapeutically. It measures factors of the extrinsic pathway (I, II, V, VII, and X). It can also be used to measure the effect vitamin K as well as diagnostic test to confirm vitamin K deficiency [23].

Vitamin K deficiency is one of the likely reasons that may be responsible for the high PT value observed among patients with renal failure in this study. Vitamin K deficiency is common among people of low social economic class and poor educated persons. Both problems are a common phenomenon in Nigeria and the North Western Region in particular. Most Nigerians living with CRF are not as privileged as their counterparts in most developed countries in the world. The WHO estimates that a significant 90.2% of Nigerians live below the poverty level of $2 per day [25], and a significant number of Nigerians are expected to bear a significant proportion (75%) of healthcare costs while the government provided only an insignificant 25.5% of the healthcare expenditure [26]. The net result of this poor stewardship by the Nigerian government is that the incidence

of complications and avoidable mortality and morbidity due to CRF will likely increase.

The incidence of CRF and complications in the African population is on the rise [24] and the economic burden associated with direct cost of intensive treatment and management associated with renal failure complications are huge and there is the fear that the African continent may struggle in managing the increasing incidence of CRF. This is likely to pose a major healthcare and economic challenges particular with the already slim health budgets, suboptimal health infrastructure and high prevalence of other endemic diseases like HIV, tuberculosis and malaria. The Nigeria government must live to her responsibility of providing quality health care service to her citizens. Access to quality healthcare in Nigeria remains a huge challenge.

Vitamin K is the collective term for compounds with vitamin K activity and having the common 2-methyl-1, 4-naphtoquinone ring structure[27]. Vitamin K occurs naturally in two forms. Phylloquinone or vitamin K1 (2-methyl-3-phytyl-15 1, 4-naphtoquinone) is synthesized by plants. Menaquinones or vitamins K2 (multi-isoprenyl- quinones) are primarily produced by bacteria. Both forms are found in animal tissues[28]. Leafy green vegetables, vegetable oils and vegetable margarines are the main sources of phylloquinone. Menaquinones are found in liver, chicken, egg yolk and certain cheeses. Natto, a fermented soybean preparation, is particularly rich in menaquinone-7 [29]. Compounds with vitamin K activity are required as cofactors for the carboxylation of glutamic acid to γ-carboxyglutamic acid (Gla) needed for the synthesis of factors II (prothrombin), VII, IX, and X, and proteins C, S, and Z, all involved in the coagulation of blood. The presence of Gla in these proteins enables them to bind calcium[30]

Vitamin K is absorbed in the jejunum and ileum. It is estimated that 80% of purified phylloquinone is absorbed. However, bioavailability from food sources is considerably less[29]. Gijsbergs et al [30] found out that the absorption of phylloquinone from food sources was 10-15% 50 of phylloquinone absorbed from tablet or suspension. Fat malabsorption decreases the absorption of vitamin K significantly and bleeding is an early sign of this condition[27]. Clinical deficiency is normally not detected after the first few months of life in otherwise healthy individuals. Deficiency has been seen in connection with malabsorption, antibiotic treatment and parenteral nutrition without vitamin K supplementation[27].

There are several reasons for poor management among Nigerian CRF patients; lack of access to quality treatment, challenge of fake drugs, suboptimal dosing, lack of affordability for drugs and for functional tests, poor adherence to therapy and the changed life style, cultural challenges and beliefs, reliance on self-medication, poor patient education, patronage of quacks and unsubstantiated unorthodox therapy. There is also the need to build the capacity of health care professionals responsible for the management of CRF patients in Nigeria. This can be achieved by providing a continuing education on CRF management to enable them provide a continually improving evidence-based quality service to their patients. The need to build capacity among clinicians in Nigeria to facilitate the delivery of improved quality care and treatment to reduce the risk of CRF-related morbidity and mortality in Nigeria cannot be overemphasized. Clinicians in Nigeria must learn from evidenced -based best practices, recommendations, international and national guidelines in the effective management of CRF patients. There is need to develop local evidenced- based coagulation profile for CRF.

The increase PT in patients with renal failure may contribute to bleeding diathesis which is an important complication of advanced uraemia though the frequency of haemorrhagic disorder in renal failure appears to be related to the degree of the uraemia[31.] Although the haemostatic defect in uraemia often is complex and may include thrombocytopenia and minor coagulation abnormalities. Decreased fibrinolytic activity and increased content of inhibitors of plasminogen activators which were found to be common in conservatively treated chronic uraemia may also have accounted for the abnormal PT in these patients[32].

In this study, we observed a decrease in the Partial Thromboplastin Time with Kaolin (PTTK) of 2.6 sec of the renal failure patients from that of the control group. This is consistent with the findings of Sanchez-Avalos and coworkers in a study which was carried out on 304 renal failure patients[33]. But our findings is inconsistent with the works of Rafiq and colleagues; Alghythan and colleagues and Anand and colleagues both of whom showed that the PTTK levels increased in renal failure patients[19,20, 21]. The decrease in PTTK could have resulted as a response to the acute phase reaction, a condition causing pronounced tissue inflammation or trauma which elevates the coagulation factor XIII. This elevated factor XIII can cause a decrease in the PTTK which measures the intrinsic and the common pathway of coagulation.

In table 2, the Mean ± standard deviation of PT of subjects males and females was compared with control males and females (16.3 ± 2.3 and 17.1 ± 3.8; 15.4 ± 1.1; and 16.0 ± 1.9 respectively) and the PTTK also was compared of the tests and control among different genders (35.0 ± 6.2 and 35.0 ± 6.4; 37.0 ± 3.9 and 35.8 ± 1.3 respectively). We observed that the variation in PT and PTTK was not significant ($p > 0.05$) across the gender, indicating that gender is not a factor that can affect the coagulation profile in kidney failure patients.

5. Conclusion

In conclusion, this study has shown that kidney failure leads to increased level of Prothrombin Time and decrease in Partial Thromboplastin Time with Kaolin. This abnormality could contribute to bleeding diathesis in patients with kidney failure. We advocate that renal failure patients should eat a balanced diet to keep their vitamin K intake consistent from day to day needs. Regular monitoring of coagulation profile of renal failure patients is also recommended.

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