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BLOOD COAGULATION AND BIOCHEMICAL PARAMETERS AMONG PATIENTS WITH NEPHROTIC SYNDROME IN SOME PARTS OF SOUTH WEST NIGERIA

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ABSTRACT

This study was carried out to assess the impact of nephrotic syndrome on some blood coagulation and biochemical parameters and to see if there is any correlation between the coagulation and biochemical parameters estimated among these group of patients some part of South West Nigeria. Sixty (60) patients with nephrotic syndrome formed the subjects for this study, while sixty (60) apparently healthy individual served as the control population. The subjects were between the ages of 3 – 60 years. Out of sixty (60) patients recruited for this work, 34(56.67%) were males while 26(43.33%) were females. Whole blood was collected from all the subjects and control to determine some of their coagulation (PT, PTTK and Pletelet) and Biochemical Parameters as well (Total Protein, Albumin, Urea and Creatinine). Also 24 hour urine was collected into 1ml of 1% normal HCL from each of the subjects and random urine samples from the control subjects for urinary protein estimation using standard methods. Data generated were analyzed using SPSS standard deviation, correlation and t-test. $P \leq 0.05$ is considered statistically significant. The results of this work showed that males were more affected than the females and the ratio of male to female was 1.9:1. The average total serum proteins of subject worked on was 55.70± 13.5g/L control subject was 70.59±11.38g/L ($p>0.05$), urinary protein 6.66±2.64g/L, control 0.72±0.28g/L ($p<0.05$), Albumin 22.72±7.23 control 40.47±7.75 ($p<0.05$), creatinine 263.92±160.73 control 58.78±17.36 ($p<0.05$). It was also found out that the PT and PTTK were affected in patient with nephrotic syndrome ($p<0.05$). The platelet count in subjects were found to be significantly reduced ($p<0.05$) in this study. Total protein (TPR) and ALB were found to be inversely correlated to PT ($p<0.05$, 0.01), UPRT and creatinine correlated positively to PT ($P<0.05$), while Creatinine correlated positively to PLT (<0.05). This study shows that nephrotic syndrome in part of south west is associated with different degrees of abnormality in coagulation and biochemical parameters and some of the biochemical parameters were correlated to PT and Platelet.

KEY WORDS: Nephrotic, Total protein, Albumin, Prothrombin Time, Partial Thromboplastin Time with Kaolin.

INTRODUCTION

Nephrotic syndrome is one of the common chronic disorders characterized by alteration of permeability of the glomerular capillary wall of bowman capsule, resulting in its inability to restrict the urinary loss of proteins [Ghodake and Suryaka, 2010). Proteinuria and hypoalbuminaemia are known to be risk factors for thromboembolic event in nephritic syndrome (Kumar *et al*., 2012) Coagulation disorders in nephrotic syndrome had been linked to the heavy proteinuria and hypoproteinaemia due to defect of the glomeruli that are being experienced by individual with this disorder. Since the majority of coagulation factors are proteins and are excretable with the urine this lead to low level of some of these proteins which directly affect the ability of the body to bring about coagulation at the normal stipulated time and result into coagulation disorder. Blood coagulation (the cessation of blood loss from a damaged vessel) is part of an important host defense mechanism.

Blood coagulation system and immune system of higher organism are thought to have a common ancestral origin. During infections, the blood coagulation system is activated and component of the haemostatic system are directly involved in the immune response and immune system modulation. It limits pathogen dissemination and

supports pathogen killing and tissue repair (Antoniak, 2018). Glomerular defect due to damage endotheial surface, the glomerular basement membrane or podocytes lead to leakage of all plasma proteins into the urine. Protein in urine greater than 3g/24hour urine or on a single spot urine collection, the presence of 2g of protein per gram of urine creatinine characterized the presence of nephrotic syndrome.(Biswas *et al*., 2009) Other characteristics include heavy proteinuria sufficiently to cause hypoalbuminaemia and usually associated with oedema, Hyperlipidemia and hyper coagulation (David, 1990). It is one of the commonest kidney diseases in the adolescent and young adult (Togawa *et al.,* 2004). The incidence tends to decrease after the age of 40 years with adult onset disease carrying the worst prognosis. It is commoner in the tropics than the temperate. It has been shown to be one of the leading causes of kigney disease in Nigeria (Akinsola, *et al*., 1984)

MATERIALS AND METHODOLOGY

This was a cross sectional study carried over ten months. A total of 120 subjects volunteered to participate in this study, clinically confirmed sixty (60) patients with nephritic syndrome and sixty (60) age-matched apparently healthy individual. Subjects were all Nigerians within the age bracket of 2½ and 60 years. The clinical features of nephrotic syndrome that distinguish it from other renal diseases are the facial and lower extremities oedema, low urine output and increase general body weight may involve. Heart failure may also present similar feature but there will be little or no proteinuria and the patient will have the history of heart disease. The Laboratory distinguishing features are the hypoproteinaemia, hypoalbuminaemia and high proteinuria greater than 3.5g/24hour urine. Structured questionnaire was administered to each participant to obtain their demographic information. Ethical clearance was granted by the Ethical Committee of Ladoke Akintola University of Technology Teaching Hospital Osogbo.

Inclusion criteria

Patients with urinary protein ≥3.5g or albumin >1.5g/24hr urine (David and Christopher, 2003).

Exclusion criteria - Patients on oral anticoagulants, those who had recent blood/blood products transfusion and recent operation were excluded.

Consent: Consents of the subjects were obtained directly from those that were above eighteen years and above while those that were below was obtained from their parents or guidance through the aid of a well-structured questionnaire.

Sample collection and processing

About 10ml of venous blood was collected by vane-puncture. 5ml was dispensed into Na^+ EDTA anticoagulant bottle for biochemical parameters estimation, 4.5ml into 0.5ml (3.8%) sodium citrate for coagulation assay. The EDTA blood samples were spun at 500g for 10 minutes, while the citrate samples were spun at 1,500g for 15 minutes, plasma separated and stored frozen at -20^{o}C until analyzed.

Urine specimen collection: A 24 hour urine sample was collected into 1ml of 1% normal HCL from each of the subjects and random urine samples from the control subject for urinary protein estimation.

Laboratory Analysis

Creatinine was estimated by Jaffes reaction described by Kazmierczak, (1996).

Henry *et al*., (1956) method of total protein was used for total protein estimation as modified by Abubakar *et al*., (2009) in this work.

Urinary total protein was estimated using turbidimetry method described by Henry *et al.,* (1956) and modified in 1983 by Bennett *et al*.,(1983)

Dacie and Lewis (2001) method was used for Prothrombin test (PT), Partial thromboplastin time test (aPTT) and platelet count

Statistical Data analysis

Data collected were analysed using the Statistical Package for Social Scientist (SPSS version 24) 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 subject. Statistical significant level was put at $p \leq 0.05$.

RESULTS

The overall Biochemical parameters of patients with nephrotic syndrome together with the control were presented in Table1. Statistically significant reduced values were observed in serum total protein (TPR) and albumin (ALB) of patients with nephrotic syndrome ($P<0.05$) while the results of urinary protein (UTPR) and creatinine (CRE) were significantly higher ($P<0.05$). Table 2 shows the results of biochemical parameters of male with nephrotic syndrome compare to the result of male without nephrotic syndrome individuals (control). The results show statistically significant reduced level of serum total protein and albumin ($P<0.05$) while the results of creatinine and urinary protein were significantly higher ($P<0.05$). The biochemical parameters of female patients with nephrotic syndrome together with the non nephrotic apparently healthy female individuals (controls) was presented in table 3. The pictures of the results seen in the female were replica of what was seen in the male with nephritic syndrome. Table 4 represents the overall result of coagulation profile among patients with nephrotic syndrome. The PT results was statistically significant higher when compare to the control ($P<0.05$) likewise the PTTK ($p<0.05$). Statistically significant low level result was obtained in PLT ($P<0.05$). Male and female coagulation results were presented in tables 5 and 6.Statistically significant higher results were seen in PT

(P<0.05) and PTTK (P<0.05) while the result of PLT was statistically significant lower (P<0.05) when compared to the control. The female results were different. Statistically significant higher result was recorded in the PT when compared to the control (P<0.05). The experimental difference seen in PTTK and PLT were not statistically significant (p>0.05).

In table 7, correlation between the coagulation and the biochemical parameters of patients with nephrotic syndrome is presented. TPR was inversely correlated to PT (r=-0.213**, P<0.05) also ALB correlated negatively with PT (r=-0.387**, P<0.01). UPRT correlated positively to PT (r=0.405**, P<0.01), likewise CRE also correlated positively to PT (r=0.235**, P<0.01). The correlation between the PLT and CRE was negative (r=0.192, P<0.05).

RESULTS AND DISCUSSION

Table 1: Biochemical parameters of patients with nephrotic syndrome and Controls.

	Results X ± SD		
Parameters	**Test Group N =60**	**Control Group N =60**	**p-value**
TPR (g/L)	55.70±13.15	70.08±11.50	<0.05
ALB (g/L)	22.72±7.23	40.47±7.75	<0.05
UPRT (g/24hr urine)	6.66±2.64	0.72±0.28	<0.05
CRE (µmol/L)	263.92±160.73	58.78±17.36	<0.05

Key
TPR = Total Protein, ALB = Albumin, UPRT = Urinary Protein, CRE = Creatinine.

Table 2: Biochemical Parameters of Male with Nephrotic Syndrome and controls.

	Results X ± SD		
Parameters	**Test Group N =34 (Male PNS)**	**Control Group N =34 (Male without NS)**	**p-value**
TRT (g/L)	54.50±13.23	70.59±11.38	<0.05
ALB (g/L)	22.24±7.11	40.91±7.90	<0.05
CRE (µmol/L)	255.85±198.41	61.24±15.41	<0.05
UPRT (g/24hr urine)	6.67±2.65	0.71±0.31	<0.05

Key
TPR = Total Protein, ALB = Albumin, UPRT = Urinary Protein, CRE = Creatinine.

Table 3: The Biochemical Parameters of Female Patients with Nephrotic Syndrome and Controls.

	Results X ± SD		
Parameters	**Test Group N =26**	**Control Group N =26**	**p-value**
TPR (g/L)	57.27±13.13	70.19±11.17	<0.05
ALB (g/L)	23.35±7.45	39.69±7.58	<0.05
CRE (µmol/L)	239.23±120.82	59.34±1.00	<0.05
UPRT (g/24hr urine)	6.63±2.70	0.74±0.23	<0.05

Key
TPR = Total Protein, ALB = Albumin, UPRT = Urinary Protein, CRE = Creatinine.

Table 4: Coagulation profiles of patients with nephrotic syndrome and the controls.

	Results X ± SD		
Parameters	**Test Group N=60**	**Control Group N=60**	**p- value**
PT (s)	14.66±2.10	13.24±0.93	<0.05
PTTK (s)	36.66±5.31	34.84±4.44	<0.05
PLT($x10^{12}$/L)	208190.00±85486.13	246930.00±8573.24	<0.05

KEY
PT = Prothrombin Time, PTTK =Partial thromboplastin with kaolin. PLT = Platelet

Table 5 Coagulation profiles of male patients with nephrotic syndrome and controls.

	Results X ± SD		
Parameters	**Test Group n=34**	**Control Group n=34**	**p- value**
PT(s)	14.95±2.34	13.11±0.93	<0.05
PTTK (s)	37.04±5.39	34.07±3.38	<0.05
PLT($x10^{12}$/L)	195470.00±80271.60	242940.00±55301.9	<0.05

KEY
PT = Prothrombin Time, PTTK =Partial thromboplastin with kaolin. PLT = Platelet

Table 6: Coagulation profile of female patients with nephrotic syndrome and controls.

	Results X ± SD		
Parameters	**Test Group n=26**	**Control Group n=26**	**p- value**
PT(s)	14.33±1.65	13.35±0.93	<0.05
PTTK (s)	35.96±5.30	36.20±5.50	>0.05
PLT(x10^{12}/L)	233350.00±76444.78	250730.00±80702.69	>0.05

KEY
PT = Prothrombin Time, PTTK =Partial thromboplastin with kaolin. PLT = Platelet

Table 7: Correlation between coagulation and biochemical parameters of patients with nephrotic syndrome.

	PT	**PTTK**	**PLT**
TPR	-.213*	-.028	-.009
ALB	-.387**	-.070	.156
UPRT	.405**	.097	-.162
CRE	.235**	.121	-.192

* Correlation is significant at 0.05
**Correlation is significant at 0.001

DISCUSION

The biochemical abnormalities associated with nephrotic syndrome such as massive proteinuria and hypoalbuminaemia were also confirmed in this report. The average total serum proteins of subject worked on was 55.70± 13.5g/L while the average of the control subject was 70.59±11.38g/L (p>0.05). This result indicates a reduced level of protein in the blood and when the urinary protein was estimated, it was discovered that the urinary protein in the patients with nephrotic syndrome (PNS) was higher than the control (p<0.05). This correlate with the findings of Adekoya *et al*, (2011) where they reported the mean 24hr urinary protein of nephrotic syndrome patients to be (7.72±3.56g/L) while the present work reported 6.66±2.64g/L as the average mean of urinary protein. The urinary protein values gotten from this report when compared to other reports appear to be lower than many other workers. Akisola *et al*, (1984) reported a mean proteinuria of 8.5g/24hrs in Ibadan, Oviasu and Ojogwu, (1992) reported a mean proteinuria of 8.16g/24hrs. Albuminuria and proteinuria was reported by Chowdhury *et al*, (2010). The abnormal result was due to high leakage of protein and albumin through the damaged basement membrane of the glomeruli in the kidney. When this continue for long the rate of synthesis of both parameters from the liver was found to be far less than the rate of linkage which will eventually leads to reduced level of both in the blood.

Based on the International Study of kidney Disease in Children (ISKDC), the decrease of serum albumin level (hypoalbuminemia) is the mandatory laboratory criteria to diagnose nephrotic syndrome, with the level less than 2.5g/dl (ISKDC, 1978). In this study, serum albumin level of nephrotic syndrome (NS) was found to be significantly reduced (p<0.05) compared to the controls. This finding was in line with some previous work done. Nasir *et al*, (2010), Adekoya *et al*, (2011), Ahmadzzadeh and Derakhshan (2007) all recorded low level of albumin (hypoalbuminaema) and increase level of urinary protein in nephrotic syndrome.

The result of biochemical parameters of male with nephrotic syndrome and the non-nephrotic syndrome male were compared, highly significant reduced level were found in both serum total protein and albumin while the result of creatinine and the urinary protein were significantly higher too. This also confirm the previous report that in nephrotic syndrome there is always reduced level of albumin, and protein in the blood which resulted into oedema and increase in the excretion of urinary protein. (Rivera *et al.*, 1998; Jay *et al*., 2013) The pattern of result obtained when the biochemical parameters of female with nephrotic syndrome were compared to their non-nephrotic syndrome female counterpart, were similar to that of the male with nephrotic syndrome.

The results of biochemical parameters of both male and female with nephrotic syndrome subjects were compared, there were no significant differences seen in all the biochemical parameters. This indicates that gender has no influence in the biochemical parameters of nephrotic syndrome. It was observed that male patient with nephrotic syndrome was more common than female which was correlated with other workers (Banerjee *et al*., 1982; David and Bernard, 1994; Jay *et al*., 2013)

The result of this work showed a positive correlation between the serum total protein and albumin indicating that as one is decreasing the other one is also decreasing and this was observed in patient with nephrotic syndrome. A negative correlation existed between serum total protein and urinary protein also between the serum albumin and urinary protein this means that as the urinary protein increases there will be reduction in total protein and albuminin in the blood. A statistically significant correlation existed between the serum

albumin and creatinine, this corroborated the previous work done by Sapartini *et al*, (2008). Nephrotic syndrome has been reported to be more common in males than in females (2:1 to 3:2) (Vogt and Avner, 2004; Shrivastava and Bagg, 2005)

Nephrotic Syndrome has been considered a hypercoagulable state, which may be complicated by thrombotic episode of the venous or arterial circulation (Citak *et al*., 2000).The present study demonstrated that the overall coagulation profiles (prothrombin time (PT) and activated partial thromboplastin time (APTT) of PNS were significantly high when compared to the apparently healthy individual(control). The implication of this is that coagulation factors found in both intrinsic and extrinsic pathway of blood coagulation and possibly in the common pathway are deficient. This is not a common occurrence for many coagulation factors to be deficient at the same time. What could have led to this might be due to the leakage of these proteins into the urine and the body cannot compensate the rate of lost with the rate of production. The result of this work agreed with the work of Ghanny *et al*, (2010), but different from the result of Farida *et al*, (2011) who reported no difference in the result of PT and aPTT. Though there was no bleeding symptom, simultaneous prolongation of both PT and aPTT suggest common coagulation pathway abnormalities.

The coagulation profiles of male nephrotic syndrome patient showed a slightly higher significant in both PT and aPTT, while the platelet was significantly lower when compared to the apparently healthy male control. The result of the female with nephrotic syndrome showed statistically significant difference only in the PT, while other parameters were not significant. This indicated that the effect of the nephrotic syndrome is more in the coagulation parameters of male with nephrotic syndrome than their female counterpart. The coagulation parameters of both were compared and there were no significant difference in all the coagulation parameters. Significant correlation existed between the prothrombin time (PT) and urinary protein together with creatinine.

Platelet is a non-nucleated cells produced from the bone marrow and actively involved in blood coagulation. In this study, platelet count in patient with nephrotic syndrome was significantly lower than the control. This was also observed when male and female subjects' platelets were compared to apparently healthy controls. This observation was contrary to the report of Farida *et al*, (2011), Mortazavi and Majidi (2008) and Ananda *et al*, (1996) where they found a significant increase in platelet counts of patients with nephrotic syndrome. Yalcinkaya *et al*, (1995) reported similar platelet count in patient with nephrotic syndrome and the control. The role of platelet in the generation of hypercoagulability seen in PNS as reported by some researchers (Sirolli *et al*., 2002) might not be due to the quantitative aspect of platelet but on the qualitative. Anand et al, (1996) stated that the various abnormalities observed in platelet functions, as well as in the release of different products (ADP, thrombin, collagen, arachidonic acid, immune complex) by platelet have been linked to increased thromboembolic phenomenon. Mittal *et al*, (2013) reported that platelet hyperaggregability is one of the mechanisms and factors which are involved in the development of thromboembolic complications in nephrotic syndrome. Hypoalbuminemia and albuminuria which are known as one of the biomarkers for nephrotic syndrome had also been reported to exert a suppressive effect on platelet functions. The mechanism of this action was reported to be due to the binding of arachidonic acid by albumin, preventing its being metabolized to thromboxcyane A2 and endoperoxidase, which are potent proaggregating substance (Bennett and Cameron, 1987; Jackson *et al*., 1982; Schieppati *et al*., 1984; Yoshida and Aoki, 1978). Other factors that are involved to contribute to the interplay in the development of thrombotic complication are the endothelia cell injury and hypercoagulability. Experimental differences seen when the female PNS platelet and female control and both male and female PNS were compared, were not statistically significant. Though the correlation between some of the biochemical parameters and platelet count from this result were not significant, inverse correlation was observed between platelet and albumin and the correlation was direct. This was contrary to Wasilewska et al (2005) where they report significant inverse correlation between PLT count and plasma albumin levels.

CONCLUSION

This study shows that nephrotic syndrome in part of South West Nigeria is associated with different degrees of abnormality in coagulation and biochemical parameters and some of the biochemical parameters were correlated to PT and Platelet.

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