

## Evaluation of C-Reactive Protein and Interleukin-6 among Nephrotic Syndrome Patients in Kano Metropolis

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### ABSTRACT

**Background:** Nephrotic syndrome (NS) is a multi-factorial clinical manifestation associated with increased glomerular permeability, proteinuria, hypoalbuminemia and dyslipidaemia, leading to cardiovascular episode among others. **Aim and objectives:** The aim of this study was to evaluate C-Reactive Protein (CRP) and Interleukin-6 (IL-6) among Nephrotic syndrome patients in Kano metropolis. the objective of this study was to determine the serum total protein, urinary proteins (UP), CRP, IL-6 and the relationship between UP with CRP and IL-6 among NS patients compared with control subjects. **Materials and Methods:** A total of 50 NS patients and 25 apparently healthy controls were recruited for the study, males and females were 32 and 18 respectively, with aged range between 4-70 years. Blood and spot urine sample were collected from each participant. Serum total protein and albumin were assayed using Biuret and bromocresol green binding method by manual colorimetric technique respectively, serum CRP and IL-6 were determined using quantitative enzyme linked immunosorbent assay technique, while UP was determined using sulphur salicylic acid. SPSS software package version 21 was used for the analysis of data. **Results:** Our finding shows that, the mean age of the patients is 15.16, male recorded higher percentage frequency of 32(64%) while female recorded a percentage frequency of 18(36%), the higher frequency of marital status and ethnic group were observed in single status and Hausa patients respectively. The mean values of UP, Serum CRP and IL-6 were significantly higher ( $p < 0.00$ ) in patients' group when compared with the controls while Total protein, Albumin, Globulin and Albumin Globulin ratio were significantly lower ( $p < 0.05$ ) in patients' when compared with the controls group. There was positive correlation between UP & CRP ( $r = 0.52$ ,  $p = 0.00$ ), UP & IL-6 ( $r = 0.69$ ,  $p = 0.00$ ) and CRP & IL-6 ( $r = 0.79$ ,  $p = 0.00$ ). **Conclusion:** Our result revealed increase serum concentrations of CRP & IL-6. Those analytes might serve as an important immunological biomarker in the management of patients with nephrotic syndrome.

**Key words:** Atherosclerosis, Biomarker; C-Reactive protein, Immunology, Interleukin-6

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## INTRODUCTION

Nephrotic syndrome (NS) is a kidney disease associated with peripheral edema, heavy proteinuria, and hypoalbuminemia, often with dyslipidaemia (1). Patients are typically presented with edema and fatigue, without evidence of heart failure or severe liver disease (2). The diagnosis of NS is based on typical clinical features with confirmation of heavy proteinuria and hypoalbuminemia (3). Nephrotic syndrome is associated with several medical complications, the most severe and potentially fatal being cardiovascular episode, bacterial infections and thromboembolism (4). The constellation of features that characterize nephrotic syndrome develops from primary alterations of the perm selectivity barrier of the glomerular capillary wall, which is no longer able to restrict the loss of protein to less than 100 mg/m<sup>2</sup> body surface per day (5).

C - reactive protein (CRP) belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins, also known as cytokine-induced “acute-phase” proteins (6,7), which is predominantly produced in the liver and to a lesser degree in the kidney (8,9). The human CRP molecule is composed of five identical non-glycosylated polypeptide subunits each containing 206 amino acid residues (7). The protomers are non-covalently associated in an annular configuration with cyclic pentameric symmetry (10). Most functions of CRP are easily understood in the context of the body’s defenses against infective agents (11). Despite structural differences with immunoglobulin molecule, CRP shares similar functional properties with the immunoglobulins, such as, the ability to promote agglutination, activation of the classical complement pathway, bacterial capsular swelling, phagocytosis and

precipitation of polycationic and polyanionic compounds (12,13).

Interleukin (IL)-6 is produced at the site of inflammation and plays a key role in the acute phase response as defined by a variety of clinical and biological features such as the production of acute phase proteins (14). IL-6 in combination with its soluble receptors IL-6R $\alpha$ , dictates the transition from acute to chronic inflammation by changing the nature of leucocyte infiltrate from polymorphonuclear neutrophils to monocyte/macrophages (15). In addition, IL-6 exerts stimulatory effects on T- and B-cells, thus favouring chronic inflammatory responses (16).

Dyslipidemia is a major risk factor for atherosclerosis, hence, patient with NS have a higher risk of vascular disease (17). Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and it has been implicated in patients with NS due to the occurrence of dyslipidemia (18). Several parameters of systemic inflammation have been identified; including levels of C-reactive protein which is elicited by an inflammatory stimulus and mediated through a complex network of cytokines, mainly IL-6 which have recently gained special attention as risk factors for cardiac and cerebrovascular events highly found in NS (19). CRP is an acute-phase protein primarily derived via IL-6–dependent hepatic biosynthesis; it plays a pivotal role in the development of atherosclerosis (17). The rationale of this study is to assess the CRP and IL-6 in nephrotic syndrome patients in Kano and this work may serve as a baseline research in using immunological biomarker in management of some of the complication of this patients.

## MATERIALS AND METHODS

The study is a cross-sectional study conducted in Aminu Kano Teaching

Hospital, (AKTH), Muhammad Abdullahi Wase Specialist Hospital (MAWSH) and Abubakar Imam Urology Centre. This comprised of fifty (50) nephrotic syndrome patient that were referred to either paediatric or Nephrology unit, their diagnosis was confirmed by both the clinical and laboratory diagnosis of NS and twenty-five (25) apparently healthy volunteers which were included as controls with participant's age range between 4-70 years. Serum total protein and albumin were assayed using Biuret and bromocresol green (BCG) binding method by manual colorimetric techniques as described by Randox brand diagnostic test kit and Serum globulin was obtained by subtraction of serum Albumin from serum total protein as described by using Randox brand diagnostic test kit (20). Urinary protein (UP) was assayed according to Turbidimetric Methods using sulphosalicylic acid as described by Yalamati et al. (21).

#### **C-Reactive Protein and Interleukin-6 analysis**

Serum CRP and IL-6 were measured by ELISA technique using reagents supplied by Kuancheng District, Changchun Jilin Province, China. The procedure was performed according to manufacturer's instructions. The assay range for CRP was 1.6 ng/ml-80 ng/ml and assay sensitivity is 0.5 ng/ml. For IL-6, assay range was 3 ng/L-200 ng/L and assay sensitivity is 0.6 ng/L.

#### **Inclusion criteria**

i) Patients with Nephrotic Syndrome within the ages of 4 – 70 years who consented to be enrolled in the study. ii) Patients with Nephrotic Syndrome who have no any underlying diseases like cardiovascular disease or hypertension among others.

#### **Exclusion Criteria**

i) Patients with Nephrotic Syndrome with any underlying diseases like HIV, hypertension, diabetes mellitus among others. ii) Pregnant women with Nephrotic syndrome.

#### **Ethical Consideration**

This study was approved by the Ethical Committee of Kano state ministry of health, with a Reference number MOH/Off/797/T.I/1384 dated 25<sup>th</sup> July, 2019. The purpose and the procedure of the study were explained to all participants and a written informed consent was obtained from the participants before samples were collected.

#### **Statistical Analysis**

Data was analysed using SPSS version 21.0 statistical software. The Mean and Standard Deviation were computed and results were expressed as Mean  $\pm$  SD. Student t-test was used to compare differences between means. Correlation was performed using Pearson's Correlation Coefficient. Statistical significance was set at  $p < 0.05$ .

#### **RESULTS**

The results obtained from the present study are presented in Tables 1-3 respectively. The socio-demographic distribution of the study participant's shows that the mean age of the patients is  $15.16 \pm 7.99$  and that of the control is  $24.64 \pm 15.84$ , The male had higher frequency of 32(64%) than the female with 18(36%) for the patients. The higher frequency of marital status was observed in single patients to be 48 with percentage frequency of 96% and the lower frequency of marital status was married patients with frequency of 2 and percentage of 4%, The higher frequency of Ethnic group was observed in Hausa patient to be 39 with percentage frequency of 78% and the lower frequency of Ethnic group in patients was 3 with a percentage frequency of 6%. The higher frequency of educational status in patients was observed in primary education to be 27 with a percentage frequency of 54% and the lower frequency of educational status was in patient who are in Tertiary school and

was found to be 2 with a percentage frequency of 4 % as depicted in Table 1.

**Table 1: Sociodemographic distribution of the study participants**

Characteristics	Patients (50)%	Controls (25)%
Age (mean ± SD)	15.16 ± 7.99	24.64 ± 15.84
<b>Gender</b>		
Male	32 (64)	12 (48)
Female	18 (36)	13 (52)
<b>Ethnicity</b>		
Hausa	39(78)	20(80)
Yoruba	5(10)	3(12)
Igbo	3(6)	1(4)
Others	3(6)	1(4)
<b>Marital status</b>		
Single	48(96)	19(67)
Married	2(4)	5(20)
Widow	0(0)	1(3)
<b>Educational level</b>		
Primary	27(54)	15(60)
Secondary	21(42)	8(32)
Tertiary	2(4)	2(8)

*n*= number of participants; %=percentage

**Table 2: Serum protein, urinary protein, CRP and IL-6 (Mean±SD) in patients and controls**

Parameter	Patients (50)	Controls (25)	<i>t</i> -value	<i>p</i> -value
Total Protein(g/l)	51.02±10.82	70.86±7.55	-8.236	0.000*
Albumin(g/l)	27.32±4.54	40.46 ±5.61	-8.798	0.000*
Globulin(g/l)	23.44±6.27	29.58±9.37	-3.063	0.002*
A/G ratio	1.24±0.39	1.58±0.84	-2.376	0.020*
Urinary protein(g/l)	3.42±0.41	0.75±0.37	23.859	0.000*
CRP (ng/ml)	2.81±1.32	0.96±0.75	13.07	0.000*
IL-6 (ng/L)	7.47±4.95	4.47±2.09	12.63	0.001*

AG= Albumin Globulin Ratio; CRP= C-reactive protein; IL-6=Interleukin 6; *p*≤ 0.05 (significant of *t*-test) for patient Vs Control for Analysis \*; *n*=Number of Subject

**Table 3: Correlation of Urinary protein, C - reactive protein and IL-6 among patients**

Parameters	Patients (n=50)	
	<i>r-value</i>	<i>p-value</i> <sup>#</sup>
UP& CRP	0.52	0.00*
UP& IL-6	0.64	0.00*
CRP & IL-6	0.79	0.00*

<sup>#</sup>=determined by Pearson's correlation; \*P= Correlation is significant at  $\leq 0.05$  levels (2-tailed); *r* = strength of correlation; *n*=Number of Subject; UP=Urinary Protein; CRP=C - reactive protein; IL-6= Interleukin-six; &= and.

Table 2 shows the serum protein, urinary protein, CRP and IL-6 (Mean  $\pm$ SD) in patients and controls. The mean  $\pm$  SD of UP (3.42 $\pm$ 0.41g/L), CRP (2.81 $\pm$ 1.32 ng/mL) and IL-6 (7.47 $\pm$ 4.95 ng/L) of patients were significantly (*p* = 0.00) higher compared with controls (0.75 $\pm$ 0.37 g/L, 0.96 $\pm$ 0.75 ng/mL and 4.47 $\pm$ 2.09 ng/L) respectively. The total protein (51.02 $\pm$ 10.82 g/L), albumin (27.32 $\pm$ 4.54 g/L), globulin (23.44 $\pm$ 6.27 g/L) and Albumin globulin ratio (A/G) (1.24 $\pm$ 0.39) of patients were significantly (*p*  $\geq$  0.05) lower when compared with corresponding values of controls (70.86 $\pm$ 7.55 g/L, 40.46  $\pm$ 5.61 g/L, 29.58 $\pm$ 9.37 g/L and 1.58 $\pm$ 0.84) respectively.

Correlation of Urinary protein, C - reactive protein and IL-6 among patients is shown in table 3. There was positive correlation between UP &CRP (*r*=0.52, *p*=0.00), UP & IL-6 (*r*=0.69, *p*=0.00) and CRP & IL-6 (*r*=0.79, *p*=0.00).

## DISCUSSION

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death and it has been implicated in patient with NS due to the occurrence of dyslipidaemia (18). Evaluation of CPR and IL-6 may be an important tool in the detection of early complication of atherosclerosis in nephrotic syndrome and may help in reducing the increase morbidity and mortality in this group

of patients (22). Hence, search for a possible way to reduce the complication associated with NS cannot be overstressed.

The study reveals that, the mean age of nephrotic syndrome patients was 15 years which indicate that most NS patients are less than 18 years. This is in accordance with the reports of Adedoyin et al. (23) in Ilorin, Obiagwu et al. (24) in Kano, Franke et al. (25) in German, Tapia and Bashir, (26) in African American and Hispanic. It is a relatively rare manifestation in Adults which occurs primarily due to a disease called focal segmental glomerulosclerosis (FSGS) and secondarily due to complication of systemic diseases, such as diabetes, high blood pressure and autoimmune disease (membrane nepropathy) (27,28).

This study, shows that, male had higher frequency of nephrotic syndrome patients than the female, a finding that is in conformity with previous reports of Adedoyin et al. (23), Abbas et al. (29), Schwartzman-Morris and Putterman (30), Chang et al.(31), Anigilaje and Adesina, (32). This observation is however in variance with the report Chan, (33) who reported equal gender distribution. This may be due to increase progression of disease in men with the exhibition of greater decrements in renal function and raised glomerular sclerosis which occurs more in male than women (30).

In the present study, it was observed that, unmarried cases were the majority of the affected patients. Onyemachi, (34) reported that, the minimum legal age of marriage in Nigeria is 18 years for girls and boys, Under the Child Rights Act 2003. This indicated that the predominant cases of NS in this study are below the age of marriage in our community and its environment.

In this finding, the higher frequency of Ethnic group with Nephrotic syndrome was observed in Hausa patients. Ibrahim, (35) reported that, the inhabitant of the ancient city of Kano which is located in North-West Nigeria are predominantly Hausa, this might explain the reason for the disparity. However, the patients in this study were of the same racial background, therefore, no racial comparison could be made.

Our finding shows that, the higher frequency of patients with primary education was observed. This is because the predominant cases with nephrotic syndrome in our environment are at their younger age which are predominantly in primary school were Primary education begins at around age 5 for the majority of Nigerians (36), and majorly consisting of six years of elementary studies (37).

The mean values of Serum total protein, albumin globulin and AG were significantly lower and urinary protein was significantly higher compared with control groups respectively. The finding is in conformity with the reports of Boerkoel et al. (3); Kaysen and Al Bander (38); Arije et al. (39); Karl et al. (40), but disagreed with the report of Gherardi et al. (41). The hallmark of nephrotic syndrome is increase in urinary excretion of albumin and other crucial proteins of lesser and intermediate molecular weight accompanied by a reduced in their serum concentration due to the inability of the body to compensate for the lost protein and its component in the urine (42). Albumin

synthesis increases at the level of mRNA synthesis in response to a decrease in serum oncotic pressure. The decrease synthesis of albumin or the selective loss of albumin from the circulation in nephrotic syndrome, explains the decrease in the proportion of AG ratio (43).

Previous study has attributed progression of atherosclerosis as a result of dyslipidaemia, hypoalbuminaemia and hyperoxidative stress, hypercoagulable state in nephrotic syndrome (17,19,44,45), with subsequent inflammation which contributes considerably to this disease complication (47). In the present study, the mean value of CRP and IL-6 were statistically higher in the patient group than the control group. Our reports agreed with Herbelin (48); Gursharan et al. (49); Panichi (50); Racki (51). Inflammation is one of the cardinal 'emerging' risk factor for cardiovascular disease (CVD) and an important feature in Nephrotic syndrome (52). Interleukin-6 is known to promote synthesis of CRP (53), its function primarily as an endocrine agent has been proposed to contribute to alterations in acute-phase reactants, with subsequent and more disparate pro-inflammatory effects (54). CRP may be involved in each of the stages by direct influencing processes such as complement activation, apoptosis vascular cell activation, monocyte recruitment, thrombosis, lipid accumulation by its ability to bind directly to LDL-C particles, especially oxidized (OXLDL) and deposited in atheromatous plaques (11,55,56,57). Liu et al. (58) reported that, vascular endothelial and smooth muscle cells produce IL-6 with functional allelic variants in the IL-6 gene are associated with CVD.

In this finding, statistically significant positive correlation was observed between UP & CRP, UP & IL-6 and between serum CRP and IL-6 This is in conformity with the findings of Gregg et al. (59) were they

reported that circulating inflammatory biomarkers, such as IL-6, CRP among others are implicated in NS. This might indicate that increased in UP may lead to increase in CRP and IL-6 in the serum and also increase in CRP may lead to increase in IL-6 in circulation.

### **CONCLUSION**

It may be inferred from the present study that; Nephrotic syndrome is associated with Increase C-reactive protein and IL-6. A significant correlation was established between UP with CRP and IL-6, also CRP and IL-6 respectively. Hence, monitoring of IL-6 and CRP as some immunological variable may be important in the management of nephrotic syndrome patients.

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