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Research article

Biochemical markers of nephrotic syndrome: An observational, cross-sectional study

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ABSTRACT

Background: Blood protein leakage, especially albumin, into the urine is the hallmark of nephrotic syndrome (NS), which poses a serious public health problem. The absence of albumin prompts the liver to produce more proteins to make up the difference. The therapeutic significance of these additional proteins in NS is not yet fully understood.

Methods: In total, 99 patients with NS and 47 persons without NS (control group) were included in this cross-sectional study. Socio-demographic and clinical information were obtained from recruits utilizing a standard questionnaire and a check of the lab order forms for individuals. Each participant had a 6-mL (6 mL) sample of venous blood taken and levels of calcium, C-reactive protein (CRP), albumin, and other proteins in the serum were assayed. The proteins in serum were separated using the electrophoresis technique, and the various fractions were then measured by a densitometer. Calculations were made for the oncotic pressure.

Results: The NS group had significantly greater levels of serum CRP, urea, alpha-2-globulin, gamma globulins, and M component than the control group ($p < 0.05$ respectively). Transferrin, total proteins, albumin, beta-1-globulins, calcium, and oncotic pressure were significantly higher in persons without NS compared to the NS group ($p < 0.05$ respectively). In addition, levels of CRP (odds ratio = 1.41, $p = 0.005$) and gamma globulin (odds ratio = 4.12, $p = 0.005$) in the blood were observed to be independent predictors in the occurrence of NS. These two factors increased the likelihood of developing NS by approximately 1.5 and 4 times, respectively.

Conclusion: Among the proteins assayed, CRP and gamma globulin were found to be predictors of NS. Nonetheless, further studies are required to understand the mechanisms associated with these serum proteins in NS.

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1. Introduction

Chronic Kidney Disease (CKD) is highly prevalent in sub-Saharan Africa and accounts for 14.6%–50% of renal disorders [1–4], and 0.35–1.34% of overall hospital admissions [5–8]. It is well known that Nephrotic syndrome (NS), characterized by chronic inflammation, and high levels of proteins in urine (i.e., 3.5 g/1.73 m^2 of body surface area per day), is a major contributing factor to the development of CKD [5,9–13]. Importantly, exacerbation of NS can lead to end-stage renal disease, which usually necessitates transplantation of kidneys and/or weekly dialysis treatments [5,14] leading to outcomes that are associated with significant health, social, familial and financial burdens.

Plasma proteins larger than 70 Kilo Dalton (kd) are known to be blocked from crossing the glomerular basement membrane in healthy kidneys by a charge- and size-selective barrier [15–18]. In contrast, damage to the glomerular basement membrane meshwork, typical in NS aetiology, may allow leakage of proteins from the blood [19–21]. For instance, it is not uncommon to see a marked increase in urine Albumin in NS. If left unabated, kidney membrane permeability can progressively increase, potentially resulting in a plethora of cardiovascular complications including coagulopathy [22,23].

Despite the different causes of NS, there is a substantial therapeutic challenge, especially in low-resource countries such as Ghana [24,25]. Accordingly, research reporting on proteinuria and oncotic pressure has a biased focus on Albumin. Because of the increased excretion of Albumin, the liver must produce more proteins vital to the upkeep of oncotic pressure. These proteins include alpha-2-macroglobulins and beta-lipoproteins [11,12]. The significance of these additional proteins in NS has not yet been fully elucidated, which could potentially have implications for the clinical management of NS. The aims of this research were twofold. 1. Determine variations in oncotic pressure, albumin, or non-albumin proteins in patients with NS and their healthier counterparts, 2. Investigate the predictors of NS development.

2. Methods

2.1. Research design, participants, and ethical consideration

The study was conducted at MDS-Lancet Laboratories Ghana Limited. The Ethics and Protocol Review Committee of the University of Ghana's College of Health Sciences (CHS) approved all procedures (ID: CHS–Et/M2-5.5/2019–2020). Before being admitted to the study, each participant gave their signed, informed consent. A total of 146 participants (99 individuals with NS and 47 healthy individuals) were recruited for this research. MDS-Lancet Laboratories clientele who had a prior diagnosis of NS and/or who had been referred for additional diagnostic tests were eligible to be recruited into the NS group. The diagnostic criteria for NS have been described in a prior publication [26]. Participants in the control group all had negative clinical and laboratory indicators for NS and had been selected after having a routine medical examination at the facility. Medical staff and researchers decided not to include participants who had pre-existing conditions like diabetes mellitus, renal disorders, immunocompromised, or individuals who had serious diseases requiring emergency medical attention.

2.2. Outcome metrics

2.2.1. Anthropometric measurements and demographic traits

Participants' demographic and clinical details were collected via a standardized questionnaire and a review of their laboratory request form. All participants had their weight and height measured to the nearest 1.0 kg (kg) and 0.005 m (m), respectively, using a standard physician's scale and a wall-mounted meter rule. To determine body mass index (BMI), we used the formula: weight/height squared (kg/m^2).

2.2.2. Laboratory procedures

A phlebotomist took 6 mL of venous blood from each of the subjects who were recruited while taking the necessary precautions to prevent hemolysis. Two milliliters of each blood sample were transferred to a tube containing ethylene diamine tetra acetic acid (EDTA), and the remaining 4 mL were transferred to a tube containing a gel separator for processing. After letting the samples in the gel separator tubes coagulate for ten to 15 min at room temperature, they were centrifuged at three thousand revolutions per minute for 10 min to obtain the sera. The collection of samples took place between the hours of 7:00 and 9:00 in the morning. Every day, a total of six samples were taken, then processed, and kept at -20° Celsius for a period of up to six months. The concentrations of urea, creatinine, calcium, albumin, and non-albumin protein fractions (alpha-1-, alpha-2-, beta-1-, beta-2-, C reactive proteins, transferrin, M component, and gamma-globulins) were measured using sera. The various proteins were also determined using an electrophoretic method, with the various protein fractions identified using a densitometer. The oncotic pressure was calculated using a formula that was previously discussed [27].

2.3. Statistical analysis

The information that was gathered was initially entered into Microsoft Excel and then transferred to Statistical Products and Services Solutions version 25 for additional analysis. A preliminary analysis was carried out to see if the data violated normality or residual independence. This was checked using the Shapiro-Wilk test of normality and the assumption was not violated ($p > 0.05$). The obtained sociodemographic, clinical, and biochemical characteristics were summarized using descriptive statistics. An independent-

sample *t*-test with an alpha level of 0.05 was used to evaluate whether there were differences in means for continuous data across the research groups. An Eta squared statistic was performed to measure the extent of the observed variations (effect size), and the results were interpreted as previously described (0.01 = minimal effect; 0.06 = moderate impact; and 0.14 = major effect) [28,29]. Lastly, to assess determinants of the occurrence of NS among the study subjects, a conditional logistic regression (to have a robust estimate of our results since the sample size was unbalanced) was carried out. We determined the *p* values, odds ratios, and confidence intervals for each predictor to establish its significance. Statistical significance was achieved when the probability value was less than 0.05.

3. Results

3.1. Demographic and clinical characteristics

Table 1 provides an overview of the demographic information as well as the clinical features of the participants. There were 51.5% ($n = 51$) and 44.7% ($n = 21$) males in the NS and control groups, respectively. In the NS group, the distribution for females was 48.5% ($n = 48$), while the control group had a distribution of 55.3% ($n = 26$). Those in the NS group had a mean age of 46.95 ± 22.19 years old, while those in the control group were 45.72 ± 16.08 years old, with corresponding mean BMI values of 23.63 ± 3.06 kg/m^2 and 25.14 ± 3.08 kg/m^2, respectively for the NS and control groups. Furthermore, the majority did not have any NS family history [84.8% ($n = 84$) in the NS group and 91.5% ($n = 43$) in the control group].

3.2. Albumin, oncotic pressure, and non-albumin protein levels in NS vs control

When compared with the control group, an independent-sample *t*-test revealed that the serum levels of C-reactive protein, urea, alpha-2-globulin, gamma globulins and M component were significantly higher among the NS group ($p < 0.05$ for all). In contrast, the NS group had lower concentrations of transferrin, total proteins, albumin, beta-1-globulin, calcium and oncotic pressure ($p < 0.05$ for all). Levels of creatinine, alpha-1-globulin and beta-2-globulins were not different between the two groups ($p > 0.05$) (Table 2).

3.3. Predictors of the incidence of NS

The findings of the binary logistic regression analysis are indicated in Table 3. Significant predictors of NS in this population

Table 1
Participant demographics and clinical (categorical) characteristics.

Variables	NS Group		Control Group		Chi-square χ^2	*p-value*
	Number (99)	%	Number (47)	%		
Gender					0.85	0.74
Male	51	51.5	21	48.0		
Female	48	48.5	26	52.0		
Marital status					17.65	0.04
Single	28	28.3	6	12.8		
Married	64	64.6	40	85.1		
Not applicable	7	7.1	1	2.1		
BMI					13.52	0.004
Underweight	9	9.09	1	2.13		
Normal weight	60	60.6	20	42.5		
Overweight	30	30.3	23	48.9		
Obese	0	0.00	3	6.38		
Occupation					6.12	0.33
Finance sector	12	12.1	4	8.5		
Trader	23	23.2	16	34.0		
Education sector	12	12.1	14	29.8		
Retired	28	28.3	9	19.1		
Student	10	10.1	3	6.4		
Not applicable	8	8.1	1	2.1		
Alcohol consumption						
Yes	45	45.5	23	48.9	0.19	0.58
No	54	54.5	24	51.1		
Family history of nephrotic syndrome						
Yes	15	15.2	4	8.5	1.24	0.27
No	84	84.8	43	91.5		

The sociodemographic and clinical characteristics of the research participants are summarized in Table 1. The frequency (No.) and percentages (%) of the data were calculated, and a p-value of 0.05 was judged significant. Age [Nephrotic Group $(\overline{X} \pm SD) = 46.95 \pm 22.19$ years; Control Group $(\overline{X} \pm SD) = 45.72 \pm 16.08$ years]; BMI [Nephrotic Group $(\overline{X} \pm SD) = 23.63 \pm 3.06$ kg/m^2; Control Group $(\overline{X} \pm SD) = 25.14 \pm 3.08$ kg/m^2]; NS is nephrotic syndrome, χ^2 is chi-square.

Table 2
A comparison of biochemical parameters of the study participants.

Variables	NS Group	Control Group	*p-value*	95% *CI*
	Mean ± S.E.M.	Mean ± S.E.M.		
C-reactive protein (mg/L)	57.65 ± 8.34	1.88 ± 0.44	<0.001	39.20–72.33
Creatinine (μmol/L)	198.96 ± 33.95	125.76 ± 28.00	0.104	−13.80 – 160.20
Urea (μmol/L)	9.34 ± 1.13	5.95 ± 0.78	0.020	0.67–6.12
Transferrin (μmol/L)	20.38 ± 0.98	33.98 ± 1.23	<0.001	−16.72–−10.47
Total proteins (g/L)	61.14 ± 1.76	68.89 ± 1.39	<0.001	−13.18–−4.32
Albumin (g/L)	26.51 ± 1.11	39.48 ± 1.18	<0.001	−16.19–−9.78
Alpha-1-globulin (g/L)	2.27 ± 0.09	1.89 ± 0.35	0.171	−0.17 – 0.92
Alpha-2-globulin (g/L)	7.28 ± 0.30	6.56 ± 0.21	0.049	−0.002 – 1.45
Beta-1-globulin (g/L)	4.83 ± 0.13	5.32 ± 0.12	0.013	−0.85–−0.14
Beta-2-globulin (g/L)	3.09 ± 0.14	3.06 ± 0.12	0.892	−0.33–−0.39
Gamma globulin (g/L)	13.14 ± 0.86	9.51 ± 0.18	<0.001	1.90–5.36
M component (g/L)	2.41 ± 1.24	0.25 ± 0.10	0.012	−0.21 – 4.75
Calcium (mmol/L)	2.08 ± 0.03	2.41 ± 0.03	<0.001	−0.42–−0.24
Oncotic pressure (mmHg)	20.02 ± 0.74	27.73 ± 0.79	<0.001	−9.86–−5.57

The biochemical characteristics of the study participants are summarized in Table 2. The mean and standard error of the mean is used to describe the data. NS is nephrotic syndrome, SEM is the standard error of the mean. Statistical significance was set at the 0.05 alpha level. CI is the confidence interval.

Table 3
Predictors for the development of NS.

Predictors	B	S.E.	Wald	p-value	OR	95% CI
CRP	0.349	0.12	7.78	0.005	1.41*	1.107–1.792
Creatinine	0.015	0.002	0.014	0.90	1.00	0.996–0.004
Urea	−0.301	0.10	8.27	0.004	0.74*	0.606–0.910
Transferrin	−0.143	0.09	2.33	0.131	0.87	0.722–1.042
Total proteins	−0.367	0.44	0.69	0.412	0.69	0.292–1.642
Albumin	0.052	0.123	0.176	0.674	1.05	0.827–1.341
Alpha-1-globulin	−0.920	0.336	7.56	0.006	0.50*	0.206–0.767
Alpha-2-globulin	0.188	0.377	0.249	0.621	1.21	0.577–2.525
Beta-1-globulin	0.614	0.588	1.092	0.302	1.85	0.584–5.847
Beta-2-globulin	−0.752	0.579	1.682	0.203	0.47	0.151–1.469
Gamma globulin	1.415	0.506	7.833	0.005	4.12*	1.528–11.091
M component	0.343	0.359	0.914	0.339	1.41	0.698–2.846
Family history of nephrotic syndrome	1.537	1.030	2.229	0.135	4.65	0.618–35.00
Alcohol consumption	0.105	0.786	0.18	0.893	1.11	0.238–5.184
Gender	0.446	0.862	0.268	0.605	1.56	0.288–8.464
Oncotic pressure	0.290	0.730	0.158	0.691	1.34	0.320–5.594
BMI	−0.485	0.189	6.589	0.010	0.62*	0.425–0.892
Calcium	−3.127	1.856	2.838	0.092	0.14	0.001–1.667

The predictors of NS among study participants have been listed in Table 3. *Statistically significant at the alpha level of 0.05; SE is standard error; OR is odds ratio; CRP is C reactive protein; BMI is body mass index.

included C-reactive protein (CRP), urea, alpha-1-globulin, gamma globulin and BMI. Raised levels of CRP (OR = 1.41, $p = 0.005$) and gamma globulin (OR = 4.12, $p = 0.005$) in the blood increased the odds of occurrence of NS by approximately one and a half and four-folds, respectively, whereas BMI (OR = 0.62, $p = 0.010$), serum levels of urea (OR = 0.74, $p = 0.004$), and alpha-1-globulin (OR = 0.50, $p = 0.006$) had less predictive power.

4. Discussion

The primary purpose of this study was to evaluate the differences between NS and healthy volunteers concerning the concentrations of albumin and non-albumin proteins like C-reactive protein, urea, transferrin, alpha-1-globulin, alpha-2-globulin, beta-1-globulins, beta-2-globulins, gamma globulins, and M component. In comparison to the control group, those with NS had significantly increased concentrations of C-reactive protein, urea, gamma globulins and alpha-2-globulins in their blood. Furthermore, the levels of transferrin, total proteins, albumin, and beta-1-globulins were significantly lower in the case group compared to the control group. This observation of high C-reactive protein and low albumin levels among participants in the NS group is consistent with prior studies. In patients with NS undergoing dialysis, previous studies report high C-reactive protein levels and decreased blood albumin levels [30–32]. It is noteworthy, that, low blood albumin levels are a significant contributor to hypocalcemia in patients with NS [33, 34] and so a compelling argument may be made that this cohort of NS patients may be at risk of hypocalcemia. Although reduced levels of albumin among NS patients have been linked to hypovolemia, the albumin levels of the NS patients in the current study, although

lower than the control group, did not appear to be associated with hypovolemia.

A further significant objective of the present investigation was to determine whether or not individuals who had been diagnosed with NS had distinct colloid osmotic pressures from those who did not have NS. According to the findings of this study, the oncotic pressure in the group that had NS was significantly lower than that of the control group. Usually, patients with NS have much lower albumin than the general population [11,12]. Some studies have suggested that albumin is responsible for maintaining colloid oncotic pressure in the majority of instances. Reports suggest that albumin accounts for approximately eighty percent of the colloid osmotic pressure [35,36], which has been attributed to the fact that its concentration is over twice that of globulin, even though it has the lowest molecular weight among the major plasma proteins. Interestingly, colloid osmotic pressure has been proposed as a control of albumin production [37,38]. Most crucially, despite much larger levels of C-reactive protein, urea, alpha-2-globulins, and gamma globulins in the NS group, they were unable to maintain colloid oncotic pressure. This appears to be yet another piece of information from the current study that supports past claims that albumins are the main proteins contributing to colloid oncotic pressure.

The third purpose of this research was to determine risk factors for NS. The chance of being diagnosed with NS rose by around 1.5 times for those with elevated C-reactive protein levels and by a factor of 4 for those with elevated gamma globulin levels. The risk of developing NS was however inversely associated with BMI and with blood levels of urea and alpha-1-globulin. Despite these aforementioned results, additional studies are required to fully elucidate predictors of the incidence of NS.

A strength of the study was the quantification of non-albumin protein fractions in sera using a densitometer, after separation by electrophoresis. Some limitations of the current study included not determining several comorbidities such as hyperlipidemia, hypertension and diabetes mellitus in recruited subjects. These comorbidities are associated with serum osmotic pressure in NS. Thus, this study cannot account for the dynamics that these comorbidities bring to NS. The authors were also unable to incorporate information on how the detected biomarkers affected overall survival since we did not conduct a follow-up with the participants. Unfortunately, our case participants' steroid therapy records were inaccessible for this investigation. This could have had an impact on the biochemical parameters measured. Additionally, urine samples were not collected and analyzed in this study, hence, may have prevented the understanding of a full picture of the epidemiology of NS. Furthermore, because this was a cross-sectional study, we were limited in our ability to determine the explanation or cause for the observed associations.

5. Conclusion

In comparison to the control group, the NS group had higher levels of C-reactive protein, urea, and gamma globulins and lower levels of transferrin, total proteins, albumins, beta-1-globulins, calcium, and colloid osmotic pressure. Elevated C-reactive protein and gamma globulin levels in the blood enhanced the likelihood of developing NS by almost one-half and four-fold respectively. Although our findings add considerably to the gaps in the pathophysiology of NS, more research is needed to understand the mechanistic elements of NS.

Ethical approval and consent to participate

The College of Health Sciences (CHS), University of Ghana, through their Ethical and Protocol Review Committee (EPRC), gave ethical permission for this study (ID: CHS–Et/M2-5.5/2019–2020). In-depth descriptions of the study's objective, risks, and benefits were given to participants. All participants signed a consent form after obtaining the necessary information.

Author contribution statement

Emmanuel Kwaku Ofori: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Egyam Bill Clinton: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Henry Asare-Anane: Conceived and designed the experiments; Wrote the paper.
Seth Dortey Amanquah: Conceived and designed the experiments; Wrote the paper.
Seth Kwabena Amponsah: Analyzed and interpreted the data; Wrote the paper.
Jayasinghe SU: Analyzed and interpreted the data; Wrote the paper.
Obed Danso Acheampong: Performed the experiments; Wrote the paper.

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Availability of data and material

The corresponding author will make the datasets that were used throughout this study available to the interested party upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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