

Assessment of Serum Copeptin Level and eGFR in Adult Hypertensive Individuals Suspected with Polycystic Kidney Disease in NAUTH, Nnewi

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Abstract

Background: Hypertension is consistently implicated in the development of chronic kidney diseases globally, though its pathologic process in the development of autosomal dominant polycystic kidney disease is still unclear. This study is a cross-sectional prospective study designed to evaluate the renal function of hypertensive individuals suspected with Polycystic kidney disease using serum Copeptin, and estimated glomerular filtration rate (eGFR) as Biomarkers. **Methods:** A simple random sampling technique was employed in the recruitment of forty (40) hypertensive patients suspected with Polycystic kidney disease (test group), and forty (40) normotensive individuals (control group), both within the age range of 25 - 90 years. Blood sample was collected and serum extracted for the analysis of these parameters using microplate ELISA and colorimetric method respectively. The serum creatinine was used to calculate for the estimated glomerular filtration rate (eGFR) for each individuals, urinalysis for urine protein, body mass index (BMI), waist-hip ratio (WHR), Systolic blood pressure (SBP) and diastolic blood pressure (DBP) for anthropometric measurements were also performed for each individuals. **Results:** Serum copeptin, was significantly higher while eGFR was significantly lower in test group compared to control group, including in gender-based comparison. The mean values of age, BMI, WHR, SBP and DBP were significantly higher in test group compared to control group, including in gender-based comparison. BNP and copeptin were significantly correlated with SBP. **Conclusively**, the significant increase in serum copeptin with decreased eGFR among hypertensive individuals strongly indicates derangement in renal

function which may suggest evidence of polycystic kidney disease and may subsequently progress to renal failure if not properly managed. The significant increases in both BMI and WHR as observed among the study group suggests overweight which is a strong risk factor of hypertension as well polycystic kidney disease.
Keywords: Polycytic Kidney disease, Copeptin, eGFR, Adults, Hypertension, Nigeria
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1. Introduction

Polycystic kidney disease (PKD) is a genetic disease that is depicted of cystic enlargement which can lead to chronic kidney disease and other degenerative renal conditions with subsequent progression to end stage renal disease (ESRD) (Murpy et al.,2019). Autosomal dominant polycystic kidney disease (ADPKD) gradually develop between 50 -60 years of life. About 2.5 % of people with end-stage renal disease is diagnosed of this ailment (Chapman, 2008; Wuthrich et al., 2009). Studies have shown that cardiovascular and cerebrovascular deaths forms the basis of increased incidences of deaths in ADPKD individuals in the post-dialysis period (Perrone et al*.,* 2001). (Chang et al., 2009). And these conditions are mostly present in these population following increase exposures to hypertension (Ecder et al., 2013). Hypertension, flank pain, hematuria, and renal cyst infections are mostly common in individuals with ADPKD (Ukibe et al. 2022).

In spite of the kidney enlargement in the affected individuals after the progressive spread of cyst, eGFR is generally preserved in these individuals till three and four decades of life (Wuthrich et al*.,* 2009). This may continue till dialysis or kidney transplantation ensues at 70 years of age. Greater percentage of individuals with ADPKD are usually asymptomatic during diagnosis with the exception of few with onset of hypertension, acute abdomen and flank pain at the ages between 30 to 50 years of age (Torres et al., 2007; Bennett, 2009). Hypertension is the greatest risk factor for ADPKD occurring in majority of the individuals contributing enormously to post renal complication and ESRD (Srivastava et al· 2014).

Previous reports have associated elevated copeptin level with kidney failure. Copeptin has been shown to exhibit some relationships with eGFR, waist hip ratio, BMI and urinary albumin/protein excretion in hypertension, PKD and CKD individuals though the mechanisms behind these are still not yet understood (Zittema et al., 2012; Ponte et al., 2015; Engelbertz et al., 2016). Our study is aimed to assess the serum copeptin and eGFR levels in adult hypertensive individuals suspected with polycystic kidney disease in Nnamdi Azikiwe University Teaching Hospital, Nnewi

2. MATERIALS AND METHODS

2.1 Study Area

The participants for this study were recruited from the nephrology clinic in Department of Medicine in Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.

2.2 Study Design

This is a case control prospective study designed to assess the serum copeptin and eGFR levels in newly adult hypertensive individuals suspected with polycystic kidney disease in Nnamdi Azikiwe University Teaching Hospital, Nnewi.

2.3 Ethical Clearance

The ethical approval for this research was obtained from Nnamdi Azikiwe University Teaching Hospital ethics committee in accordance with the Helsinki declaration by the World Medical Association (WMA) on the ethical principles for medical research involving human subjects. Also, permission to extract information (age, gender, BMI, SBP, and DBP) from the patients' record relevant to this study was also obtained.

2.4 Sampling Technique

The participants were selected by random sampling techniques. Forty (40) adult hypertensive individuals suspected with PKD from the Nephrology clinic in Department of Medicine in Nnamdi Azikiwe University Teaching Hospital, Nnewi, and forty (40) apparently healthy individuals from staff, Nnewi Anambra State were recruited for this study.

2.5 Inclusion and Exclusion Criteria

Newly diagnosed Adult hypertensive individuals suspected with PKD and apparently healthy individuals between the ages of 25 -90 years were recruited for the study. Individuals less than 18 years of age and without evidence of PKD and patients who are unwilling to participate were excluded.

2.6 Informed Consent
Written informed consent was obtained from each study participants before recruiting them into the study.

2.7 Collection of samples
About 5ml of blood sample was aseptically collected by venipuncture from each individual into a plain blood sample container and allowed to clot, retract, centrifuged for at least 5 minutes at 3000 r.p.m. and then separated and transferred into another plain bottle and stored at -20 ºC until assayed for the study parameters.

2.8 Laboratory Analysis
Determination of Serum Copeptin was done using immunoassay method as were described by Morgenthaler et al.,(2006) while, Serum creatinine was done using Colorimetric method by Bartels & Bohmer, (1972). eGFR was estimated using calculation described by Levey, (2007) and Urinalysis test for Protein was done using Combi 9 reagent strip method by (Macherey-Nagel, 2014)

2.9 Anthropometric Measurements
Body Mass Index was calculated using the following formula: BMI = weight (kg)/meter square (m^2) While, Waist-Hip Ratio was calculated as waist measurement divided by hip measurement (W / H) in centimeter as described by WHO, (2012). Blood pressure was measured using auscultatory method as described by Berger, (2001).

2.10 Statistical Analysis
The statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 25. The results obtained from the study were analyzed using independent t- test, ANOVA, frequency tables, and Pearson's correlation. Level of significance was set at $p \leq 0.05$.

3. RESULTS
3.1 Characteristics of the study groups.
This study was aimed at evaluating the renal function of hypertensive individuals suspected of Polycystic kidney disease using serum copeptin and estimated glomerular filtration rate (eGFR) as biomarkers. A total of 80 subjects were recruited such that 40 (50.00%) for test group and 40 (50.00%) for control group. In similar fashion, out of the 40 participants recruited in each group 21 (52.50%) were males and 19 (47.50%) were females in each group. The gender (male and female) per each group (test and control) were analyzed using frequency table. The table also shows the means and standard deviations of the age, body mass index (BMI), waist-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) of both test and control groups which were analyzed and compared using independent samples *t*-test (significance set at $p \leq 0.05$). There were statistical significant differences ($p \leq 0.01$) in the age, BMI, WHR, SBP, and DBP of the study groups with that of the test group higher than that of the control group in all the parameters (see Table 1).

3.2 Health assessment of the study groups
The results showed that none (0.00%) of the control subjects have any health issue regarding the health assessment parameters used in this study. Forty (40) of the test subjects (100.00%) are hypertensive and usually have protein in urine, recurrent headache, dizziness, and abdominal or side pain. Fourteen (14) of the test subjects (35.00%) experience nausea, vomiting, and loss of appetite. Eight (8) of the test subjects (20.00%) are diabetic, have elevated BUN creatinine and often nose bleeding. Seven (7) of the test subjects (17.50%) have being on hypertensive medication and usually have blur vision. Four (4) of the test subjects (10.00%) have history of kidney stone and recurrent kidney infection. However, only one (1) of the test subjects (2.50%) claim to have family history of polycystic kidney disease (PKD) and was diagnosed of autosomal dominant type of PKD (ADPKD), undergone kidney cyst aspiration, hernia surgery once, dialysis and even kidney transplant (see Table 2).

3.3 Comparison of the copeptin level and estimated glomerular filtration rate (eGFR) between the study groups.
The results showed significantly higher level of copeptin level with lower eGFR in the test group when compare with control group ($p \leq 0.01$; see table 3)

3.4 Comparison of serum copeptin, eGFR, age, BMI, WHR, SBP, DBP levels in male test participants and control groups
The mean serum copeptin level, age, BMI, WHR, SBP and DBP in male test participants were significantly higher when compared with that of control group ($p \leq 0.01$) except for BMI ($p > 0.05$). While the eGFR of the male test participants was significantly lower when compared with control counterparts ($p \leq 0.01$; see Table 4).

3.5 Comparison of serum copeptin, eGFR, age, BMI, WHR, SBP, DBP levels in female test participants and control groups

The mean copeptin level, age, BMI, WHR, SBP and DBP in female test participants were significantly higher while eGFR was significantly lower than that of the female control group ($p \leq 0.01$ respectively; see Table 5)

3.6 Correlations with the serum copeptin in the test group

Key: Pearson bivariate correlation (r) test with significance set at $p \leq 0.05$; BMI - body mass index; WHR - waist-hip ratio; SBP - systolic blood pressure; and DBP - diastolic blood pressure; Strong positive linear relationship ($0.50 \leq r \leq 1.00$); Weak positive linear relationship ($0.00 < r < 0.50$); Strong negative linear relationship ($-0.50 \leq r \leq -1.00$); Weak negative linear relationship ($-0.00 < r < -0.50$); No linear relationship ($r = 0.00$)

4 Discussion

In this present study out of 40 hypertensive subjects; 1(2.50%) of the hypertensive subjects have undergone dialysis and 1(2.50%) had kidney transplant. This result correlates with the treatment and management of PKD (Chapman et al., 2008). 1(2.50%) of the hypertensive subjects had hematuria and 4(10.00%) had recurrent kidney infections and this results with signs and symptoms of PKD (Gabow et al., 2002). Although symptomatic lower urinary tract infections are much more common in those with ADPKD than in the general population, the pattern of the infections (more common in women) and the infectious organisms (gram-negative bacteria) are similar to those in the general population (Johnson, 2000).

Results also showed that 4(10.00%) of hypertensive subjects had kidney stones which is twice more common in those with PKD than in the general population (Granthman, 2008; Ukibe et al., 2022). Result showed as well that 20(50.00%) of the hypertensive subjects experienced abdominal or side pain and previous works reported that pain is the most common symptoms in those with PKD and may present as back, chest, abdominal, or flank pain, or a combination (Bajwa et al., 2004). Eight (20.00%) of the hypertensive subjects of this study reported elevated BUN creatinine. At the onset of PKD, serum creatinine is normally within the normal range but gradually rises as the cystic damage to the kidney becomes more severe (Horie et al 201). A possible explanation for this might be due to the role of the antidiuretic hormone (arginine-vasopressin - AVP) in hypertension and PKD, through its vasoconstrictor and antidiuretic effects. As our study observed a significant increase in serum copetin level with decreased eGFR in hypertensive individuals, AVP are often produced to regulate its severity, while in chronic kidney disease such as polycystic kidney disease (PKD), the AVP system is activated due to impaired urine concentrating capacity to maintain water homeostasis (Afsar, 2017). Being an unstable peptide, it is cleavage to produce a more stable peptide which lead to increased copeptin level (Bolignano et al., 2014). This represents the prognostic value of copetin as a good marker of kidney function in hypertension as well as PKD as was observed in this study.

Diagnosis, prognosis and treatment in chronic kidney disease is often informed by an estimate of the glumerular filtration rate (eGFR). Commonly used GFR estimation (eGFR) equations are based on serum creatinine concentrations and display suboptimal precision and accuracy (White et al., 2019). This study recorded a significant lower eGFR in the hypertensive subjects compared to the control group, which was still observed under gender-based comparison between the test group and control group. This is expected as the test participants are hypertensive patients suspected with PKD. PKD impaired the kidney function, which part of its diagnosis is decline in eGFR (Brosnahan et al., 2018). Numerous studies show that the relationship of low eGFR with the subsequent development of kidney failure is very strong, graded, independent, and consistent across populations irrespective of age, sex, race, presence or absence of hypertension and diabetes, level of albuminuria, and cause of kidney disease (Levey et al., 2015). Li and colleagues also observed significant and independent relationship between copeptin and eGFR (Li et al., 2013). Also, all the test participants (100%) had abdominal pain and urine protein which are typical for PKD and confirm the finding of declining renal function in the present study (Ponte et al., 2015; Perrone et al., 2021).

Other risk factors including age, BMI, WHR, SBP and DBP have been previously diagnosed in hypertension. This condition was further described as a universal feature of human aging (Buford et al., 2016). Also, Schrier *et al*., (2011) claimed that PKD are often diagnosed in adulthood, between the ages of 30 and 50, which coincides with the increased risk of hypertension. Hence, the significantly high mean age of the test participants (including gender-based comparison) as observed in the present study.

This study showed a significantly higher mean BMI and WHR in the test participants when compared with control group. BMI and WHR are determinants of overweight/obesity. Several mechanisms had been proposed concerning overweight or obesity related hypertension and PKD. One of these mechanisms that seem to be linked to hypertension is based on sodium retention as a result of increase in renal tubular reabsorption which causes the extracellular-fluid volume to expand (Jiang et al., 206). Also the compensatory mechanism of hyper filtration which occurs to meet the heightened metabolic demands of the increased body weight. The increase in

intraglomerular pressure can damage the kidney structure and raise the risk of developing PKD in future (Kovesdy *et al*., 2017).

Interestingly, the gender comparison of WHR and BMI in this study also maintain the significant high mean value, in both male and female test group when compared with their corresponding gender in the control group. The different observation seen with BMI and WHR under gender may be attributed to the difference in their application, as WHR measure the abdominal fat, and BMI measures the general body fats (Chinedu et al., 2013). This is also why many researchers indicated that WHR is superior to BMI in predicting CKD as it measures the abdominal changes which may be contributed by the changes in the size of the kidney in PKD (Cai et al., 2021).

The mean age of hypertensive subjects was significantly higher compared with control value, this correlates with previous study by (Chapman *et al.,* 2008). Findings also showed mean age was significantly higher in female hypertensive when compared with female control. Polycystic kidney disease is characterized by slow enlargement of the kidney with renal failure occurring by the fifth-sixth decade (50-60 years) of life. Cyst development and growth is gradual, yet despite the massive growth of the kidneys, the glomerular filtration rate (GFR) in these patients is typically conserved until ages 30-40, followed by a rapid, linear decline after this time. By the age of 70, 50% of patients with PKD will require dialysis or kidney transplantation (Cho et al., 2017). Moreover, age is a significant factor for chronic kidney diseases due to increasing prevalence of traditional risk factors for chronic kidney diseases such as diabetes, hypertension and cardiovascular diseases.

Results from this study shows that the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in hypertensive groups (including male and female) compared with control group, of course this result was expected because the test subjects are known to be hypertensive prior to this study. Blood pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP), measure the force of blood against artery walls. An elevated blood pressure (SBP and DBP) is the measure of hypertension. SBP and DBP in this study were significantly high in the test group than in control group, even when further compared based on gender. This is expected because the test group are hypertensive patients and only 17.50% were on hypertensive medication, which explains the reason for the varied symptoms, such as recurrent headache, nose bleeding, blur vision, dizziness, loss of appetite, nausea, and vomiting, as their prevalence is believed to vary according to the severity of the hypertension. Elevated SBP and DBP which is hypertension, is a serious medical condition that significantly increase the risks of heart, brain, kidney and other diseases (Tackling and Borhade, 2022. PKD associated hypertension is ubiquitous and multi-factorial with different mechanisms, such as the deleterious effects that increased blood pressure has on kidney vasculature in terms of constriction and narrowing of the blood vessels, and glomeruli becoming sclerotic (Weldegiorgis & Woodward, 2020). Hypertension is the most common manifestation of PKD and contributes to renal dysfunction and cardiovascular complications, which are the most common causes of death in those with PKD (Chapman et al., 2010).

5 Conclusion

In the present study, the changes observed in serum copeptin and eGFR levels signifies derangement in renal function which suggests evidence of PKD and may progress to end stage renal disease if neglected. Also significant increase in both BMI and WHR observed among the study group simply implies that the affected individuals are either overweight or obsessed which is a strong risk factor to hypertension. Close monitoring of renal function is recommended, as antihypertensive doses may need to be adjusted if renal function declines. Frequency of follow-up of patients should be adjusted to their symptom manifestations.

More longitudinal studies on prevalence of polycystic kidney disease in the study environment are recommended. Sensitive predictors of PKD such as computed tomography (CT) and ultrasound imaging is highly recommended for a definitive diagnosis of PKD among hypertensive subjects.

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Table 1: Health assessment of the study groups

Parameters	Test group(n=40)	Control group(n=40)
Recurrent headache	20 (50.00%)	0 (0.00%)
Dizziness	10 (25.00%)	0 (0.00%)
Nose bleeding	8 (20.00%)	0 (0.00%)
Blur vision	7 (17.50%)	0 (0.00%)
Nausea, vomiting or loss of appetite	14 (35.00%)	0 (0.00%)
Abdominal or side pain	20 (50.00%)	0 (0.00%)
Single symptoms	26 (65.00%)	0 (0.00%)
Double symptoms	20 (50.00%)	0 (0.00%)
Multiple symptoms	6 (15.00%)	0 (0.00%)
History of kidney stone	4 (10.00%)	0 (0.00%)
Haematuria	1 (2.50%)	0 (0.00%)
Recurrent kidney infections	4 (10.00%)	0 (0.00%)
Elevated BUN creatinine	8 (20.00%)	0 (0.00%)
Hypertensive	40 (100.00%)	0 (0.00%)
Diabetic	8 (20.00%)	0 (0.00%)
Urine protein	40 (100.00%)	0 (0.00%)
Being on any hypertensive medication	7 (17.50%)	0 (0.00%)
Family history of Poly cystic kidney disease	1 (2.50%)	0 (0.00%)
Type of PKD diagnosed - (ADPKD)	1 (2.50%)	0 (0.00%)
Undergone kidney cystic aspiration	1 (2.50%)	0 (0.00%)
Undergone surgery (hernia once)	1 (2.50%)	0 (0.00%)
Undergone dialysis	1 (2.50%)	0 (0.00%)
Undergone kidney transplant	1 (2.50%)	0 (0.00%)

Key: Statistical analysis – frequency table; ADPKD – autosomal dominant polycystic kidney disease; PKD – polycystic kidney disease

Table 2: Characteristics of the study groups

Parameters	Test group(n=40)	Control group (n=40)	*t*-value	*p*-value
No. of subjects	40(50.00%)	40(50.00%)		
Gender				
Male	21(52.50%)	21(52.50%)		
Female	19(47.50%)	19(47.50%)		
Age (Years)	63.70 ± 14.65	37.05 ± 12.38	8.786	0.000**
BMI (kg/m^2)	27.27 ± 2.00	24.78 ± 4.29	3.327	0.000**
WHR	1.06 ± 0.09	0.82 ± 0.06	13.956	0.000**
SBP (mm/Hg)	147.20 ± 15.37	118.15 ± 5.88	11.168	0.000**
DBP (mm/Hg)	86.33 ± 5.47	79.78 ± 6.93	4.691	0.00**

Key: Statistical analysis – frequency table and independent samples *t*-test (significance set at $p \leq 0.05$); "a" - value reported in mean and standard deviation; "**" - Statistically significant at $p \leq 0.01$; BMI - body mass index; WHR - waist-hip ratio; SBP - systolic blood pressure; and DBP-e diastolic blood pressure

Table 3: Comparison of the copeptin level and eGFR between the study groups

Groups	No of Subjects	Mean ± SD	
		Copeptin (pg/ml)	eGFR (ml/min/1.73)
Control group	40	528.21 ± 48.91	109.63 ± 10.36
Test group	40	835.68 ± 111.47	68.80 ± 22.95
***t*-value**		-15.975	10.255
***p*-value**		0.000**	0.000**

Key: Statistical analysis – independent samples *t*-test (significance set at $p \leq 0.05$); "**" - Statistically significant at $p \leq 0.01$; SD – standard deviation.

Table 4: Comparison of the age, BMI, WHR, SBP, DBP, copeptin level and eGFR between male test subjects and male control groups

Parameters	Male test subjects (n=21)	Male control subjects (n=21)	*t*-value	*p*-value
Copeptin (pg/ml)	848.74 ± 113.02	558.44 ± 41.45	11.051	0.000**
eGFR (ml/min/1.73)	66.29 ± 23.74	114.48 ± 9.70	-8.609	0.000**
Age (Years)	67.95 ± 11.07	39.81 ± 14.61	7.037	0.000**
BMI (kg/m^2)	27.57 ± 2.37	25.39 ± 4.55	1.947	0.059**
WHR	1.08 ± 0.06	0.83 ± 0.07	12.619	0.000**
SBP (mm/Hg)	148.05 ± 16.64	119.33 ± 5.22	7.545	0.000**
DBP (mm/Hg)	85.76 ± 5.49	7.31 ± 5.49	2.938	0.005**

Key: Statistical analysis –independent samples *t*-test (significance set at $p \leq 0.05$); "**" - Statistically significant at $p \leq 0.01$; BMI - body mass index; WHR - waist-hip ratio; SBP - systolic blood pressure; and DBP - diastolic blood pressure

Table 5: Comparison of serum copeptin level, eGFR age, BMI, WHR, SBP, DBP in female test participants and control participants.

Parameters	Female test group (n=19)	Female control group (n=19)	*t*-value	*p*-value
Copeptin (pg/ml)	821.23 ± 110.94	494.80 ± 32.08	12.320	0.000**
eGFR (ml/min/1.73)	71.58 ± 22.34	104.26 ± 8.37	-5.972	0.000**
Age (Years)	59.00 ± 16.87	34.00 ± 8.74	5.735	0.000**
BMI (kg/m^2)	26.94 ± 1.48	24.11 ± 3.98	2.899	0.006**
WHR	1.03 ± 0.11	0.80 ± 0.05	8.357	0.000**
SBP (mm/Hg)	146.26 ± 14.22	116.84 ± 6.41	11.155	0.000**
DBP (mm/Hg)	86.95 ± 5.54	79.63 ± 6.69	3.672	0.001**

Key: Statistical analysis –independent samples *t*-test (significance set at $p \leq 0.05$); "**" - Statistically significant at $p \leq 0.01$; BMI - body mass index; WHR - waist-hip ratio; SBP - systolic blood pressure; and DBP - diastolic blood pressure

Table 6: Correlations of the study parameters in test group

Groups	Copeptin *r*-value (*p*-value)	Remark
eGFR (ml/min/1.73)	-0.237 (0.142)	Weak negative linear relationship
Age (Years)	0.017 (0.917)	Weak positive linear relationship
BMI (kg/m^2)	0.178 (0.272)	Weak positive linear relationship
WHR	0.337 (0.033)	Weak positive linear relationship
SBP (mm/Hg)	0.544 (0.000**)	Strong positive linear relationship
DBP (mm/Hg)	0.267 (0.095)	Weak positive linear relationship

There were weak positive linear relationship ($0.00 < r < 0.50$) between copeptin and age, BMI, WHR, and DBP which were not statistically significant ($p > 0.05$). But, correlation of eGFR with copeptin sowed a weak negative linear relationship ($-0.00 < r < -0.500$) which was not statistically significant ($p > 0.05$). However, there was a significant positive correlation ($0.50 \leq r \leq 1.00$) between copeptin and SBP which was statistically significant ($p \leq 0.01$; see Table 6).