Original Article

Copeptin as a potential biomarker of chronic kidney disease to predict the disease progression in children with chronic kidney disease

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Abstract

Background: Biomarkers to predict the onset and progression of chronic kidney disease (CKD) in children are lacking, and no such definite biomarkers have been implicated in the diagnosis of CKD. We conducted this study to evaluate copeptin as a CKD marker and predict the disease progression by estimating the copeptin levels at baseline and 12 months follow-up in children with CKD stage 2 and above. **Materials and Methods:** This prospective single-centre cohort study was conducted in children under 14 years with CKD stages 2-4. Blood and urine samples were collected at enrolment and 1-year follow-up for routine investigations and serum copeptin, cystatin C and urinary neutrophil gelatinase-associated lipocalcin (uNGAL) estimation. **Results:** A total of 110 children (60 cases and 50 controls) were enrolled in the study. The mean estimated glomerular filtration rate (eGFR) of cases was 58.3 ± 18.7 ml/min/1.73 m^2. Among the cases, there was a significant rise in the serum copeptin levels from baseline 483.08 ± 319.2 pg/ml to follow-up at 1 year, that is, 1046.82 ± 823.53 pg/ml ($P < 0.0001$). A significant difference was noted in the baseline values of serum cystatin C, that is, 1512.98 ± 643.77 ng/ml and 719.68 ± 106.96 ng/ml ($P < 0.0001$), and uNGAL, that is, 13.53 ± 11.72 and 1.76 ± 2.37 ng/ml ($P < 0.0001$) between the cases and controls. There was no significant correlation (correlation coefficient = 0.10) between change in eGFR and copeptin levels during 12 months of follow-up. **Conclusion:** No significant correlation was found between the change in eGFR and copeptin levels during 12 months of follow-up. This can be due to the slow deterioration of renal functions, as most of the cases had underlying congenital anomalies of the kidney and urinary tract (CAKUT), which is known to have a slow progression of CKD and a small sample size.

Keywords: Biomarkers, children, chronic kidney disease, copeptin

Introduction

Chronic kidney disease (CKD) is associated with a decline in glomerular filtration rate (GFR) and is the major cause of debilitating disease in children. It is usually a progressive disease that frequently leads to end-stage kidney disease (ESKD).[1] It is, therefore, imperative to diagnose CKD as soon as possible and prevent its progression by initiating proper treatment in a timely manner. Serum creatinine is a well-established biomarker of renal function; however, it is affected by other factors such as age, gender, muscle mass and liver function and therefore lacks sensitivity.[2] In addition, it is elevated when there is already a significant underlying renal impairment, which hinders the early use of potential therapeutic management of CKD. The currently available common biomarkers for CKD, such as serum creatinine, urine protein and others, have their own limitations.[3] It is important to have a reliable and sensitive biomarker that can

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detect early and predict the progression of the disease for the proper management of children with CKD.

Copeptin, a surrogate marker of arginine vasopressin (AVP), is partially cleared by the kidneys. In CKD or ESKD patients, a positive association of copeptin with a decline in kidney function was observed, and the level of copeptin was elevated compared to those with normal kidney function.[4] A higher copeptin concentration was associated with kidney function decline during follow-up in patients with autosomal dominant polycystic kidney disease (ADPKD) and Type 2 diabetes mellitus, suggesting that copeptin may be a new marker to predict kidney outcome.[5,6]

Definite biomarkers to predict the onset and progression of CKD and its adverse outcomes in children are lacking, and various studies have been performed to determine the appropriate biomarkers for CKD.[3] However, no such definite biomarkers have been implicated in the diagnosis of CKD, and the results have been inconclusive. Our study aimed to evaluate if serum copeptin can be used as a marker of CKD and to predict the progression of CKD in children.

Materials and Methods

This was a prospective, single-centre cohort study to evaluate copeptin as a potential marker of CKD. Children aged 1–14 years with CKD Stages 2-4 based on the KDIGO guidelines were enrolled as cases.[7] Healthy children attending vaccination clinics or siblings of patients served as control groups. The estimated glomerular filtration rate (eGFR) was calculated using the Bedside Schwartz formula from the CKiD study.[8] CKiD equation was used to calculate eGFRCr and eGFRCys.[9]

Approximately 3 ml of blood and 10 ml of urine were collected from the cases and controls and centrifuged at 3000 rpm for 10 min. The serum was separated and stored at −80°C, and the analysis for estimating serum levels of copeptin and cystatin C was done within 6 months of the sample collection. The urine supernatant was collected and stored at −80°C, and the analysis for estimation of urinary neutrophil gelatinase-associated lipocalcin (uNGAL) was done within 6 months of the sample collection. To estimate the levels of serum copeptin, cystatin C and uNGAL, commercially available enzyme-linked immunosorbent assay (ELISA) kits (Human Lipocalcin-2/NGAL, Quantikine ELISA kit, R and D Systems Inc.; Human Cystatin C, Quantikine ELISA kit, R and D Systems Inc. and Human CPP (Copeptin) ELISA kit, Novus Biologicals) was used as per the manufacturer's guidelines, and their levels were estimated with Infinite M200PRO ELISA reader, make TECAN. The coefficient of variation for copeptin ranged from 4.49 to 5.91%, and the measurement limit ranged from 31.25 to 2000 pg/mL. The coefficient of variation for cystatin C ranged from 3.1 to 6.6%, and the measurement limit ranged from 0.030 to 0.227 ng/mL. The mean minimal detectable dose was 0.102 ng/mL. The coefficient of variation for Human Lipocalcin-2/NGAL ranged from 3.1 to 4.4%, and the measurement limit ranged from 0.003 to 0.040 ng/mL. The mean minimal detectable dose was 0.012 ng/mL.

The other routine investigations, such as blood urea, serum creatinine, serum electrolytes, uric acid, calcium, phosphate, alkaline phosphate, serum parathormone and vitamin D3, blood pH, hemogram and urine for estimation of proteinuria, were done. The same investigations were repeated at the 1-year follow-up visit. A detailed performa was filled up, including the case's history and examination results. The following investigations were performed in the controls as a part of the work-up, that is, serum creatinine, urea, uric acid, sodium, potassium, calcium, phosphate, alkaline phosphate, albumin, cholesterol, hemogram, blood pH, spot urine protein/creatinine ratio or urine protein by dipstick, uNGAL and serum levels of copeptin and cystatin C.

Statistical analysis

Data were analyzed using SPSS software version 26.0. Categorical variables were expressed in terms of frequency. Continuous variables were expressed as mean and standard deviation or median with interquartile range. Dichotomous variables were compared using the Chi-square/Fisher's exact test. Continuous variables were analyzed using the paired T-test or Wilcoxon signed-rank test.

Results

Patient characteristics

One hundred and ten children were enrolled in the study (60 cases and 50 controls). The male-to-female ratio in cases and controls was 57:3 and 33:17, respectively. The median age for cases and controls was 84 (IQR: 46.7-132) and 77.5 (IQR: 43.5-101.5) months. The diagnosis of CKD was congenital anomalies of the kidney and urinary tract (CAKUT) in all cases. Among the cases, 34 (57%) had stage 2 CKD, 21 (35%) had stage 3 CKD and only 5 (8%) had stage 4 CKD.

Biochemical indices

The mean eGFR of cases was 58.3 ± 18.7 ml/min/1.73 m^2. Serum creatinine-based renal clearance decreased from median eGFR 85 (59-155) to 63 (39-81) ml/min/1.73 m^2 at the end of 12 months follow-up. Although this difference was statistically insignificant ($P = 0.97$), there was a significant difference in the mean blood urea and serum creatinine between the cases and controls. The mean blood urea in cases and controls were 43.2 ± 22.1 and 25.66 ± 8 mg/dL ($P < 0.001$), and the mean serum creatinine in cases and controls was 0.93 ± 0.55 and 0.27 ± 0.09 mg/dL ($P < 0.001$). There was no difference in the baseline serum copeptin values between the cases and controls, that is, 483.08 ± 319.2 and 440.27 ± 179.32 pg/ml ($P = 0.21$). However, a significant difference was noted in the baseline values of serum cystatin C, that is, 1512.98 ± 643.77 and 719.68 ± 106.96 ng/ml ($P < 0.0001$) and uNGAL, that is, 13.53 ± 11.72 and 1.76 ± 2.37 ng/ml ($P < 0.0001$) between the

cases and controls. The baseline characteristics of cases and controls are depicted in Table 1.

The comparison of copeptin, NGAL and cystatin C at baseline and 1-year follow-up in cases are shown in Table 2. Among the cases, there was a significant rise in the serum copeptin levels from baseline 483.08 ± 319.2 pg/ml to Follow up at 1 year, 1046.82 ± 823.53 pg/ml ($P < 0.0001$). We found that serum cystatin C level increased from 1512.98 ± 643.77 ng/mL to 1841.91 ± 727.69 during 1-year follow-up in cases. However, no difference was seen in uNGAL from baseline to 1-year follow-up.

We did not find any significant correlation (correlation coefficient = 0.10) between change in eGFR and copeptin levels during 12 months of follow-up in children with CKD stages 2, 3, and 4 [Table 3 and Figure 1]. Similarly, we found no significant correlation (correlation coefficient = 0.03) between change in eGFR and cystatin C levels during 12 months of follow-up in children with CKD stages 2, 3, and 4.

Discussion

In the present study, serum copeptin concentration was significantly elevated in all the cases of CKD at 1-year follow-up compared to the baseline values. To the best of our knowledge, our study is the first to assess the association of baseline copeptin levels with follow-up levels at 1 year in children with CKD.

The increased levels of copeptin with the progression of CKD have been demonstrated in the literature.[10-12] In patients with Type 2 diabetes mellitus and ADPKD, a higher copeptin concentration was associated with kidney function decline during follow-up in patients, suggesting that copeptin may be a new marker to predict kidney outcome.[5,6] It has been shown that the serum concentration of copeptin depends directly on renal functions. A study by Engelbertz C *et al.*[13] demonstrated that copeptin values increased significantly with decreasing eGFR and can be used as a prognostic marker for CKD. In a study by Tasevska I *et al.*,[11] copeptin independently predicted the development of new-onset CKD and a faster decline in eGFR over time in the general population.

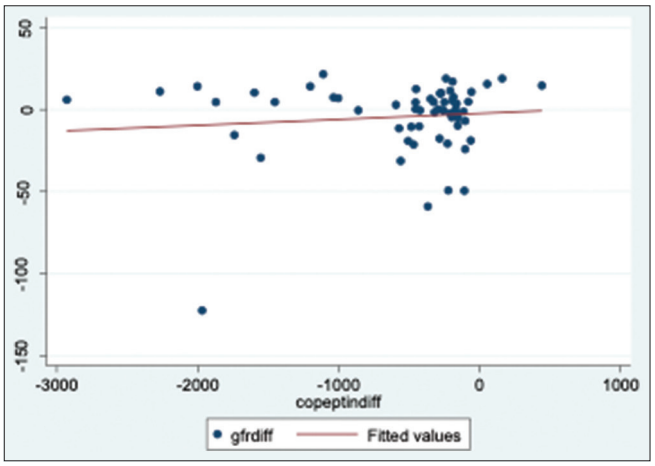

Figure 1: Correlation between eGFR difference and copeptin difference

Table 1: Baseline characteristics of cases and controls

Variables	Cases (60)	Controls (50)	*P*
Age	84 (IQR: 46.7−132)	77.5 (IQR: 43.5−101.5)	
Sex	Male: 57 Female: 3	Male: 33 Female: 17	
Diagnosis (CAKUT)	60	-	
CKD stages		-	
Stage 2	34		
Stage 3	21		
Stage 4	5		
eGFR (mean±SD) (ml/min/1.73 m^2)	58.3±18.7	-	
Blood urea (baseline) (mean±SD) (mg/dL)	43.2±22.1	25.66±8	<0.001
Creatinine (baseline) (mean±SD) (mg/dL)	0.93±0.55	0.27±0.09	<0.001
Calcium (baseline) (mean±SD) (mg/dL)	9.44±0.57	9.45±0.45	0.25
Phosphorus (baseline) (mean±SD) (mg/dL)	4.51±0.9	4.06±0.46	0.0002
Alkaline phosphatase (U/L)	252.0±75.1	226.7±65.4	0.10
Uric acid (baseline) (mean±SD) (mg/dL)	4.87±1.37	3.67±0.63	<0.001
Vitamin D (25(OH) D3) (baseline) (mean±SD) (ng/ml)	27.4±16.5	-	
PTH (baseline) (median) (pg/ml)	57.9 (IQR: 37.9−85.4)	-	
Albumin (baseline) (mean±SD) (g/dL)	5.77±3.95	4.11±0.21	0.18
Sodium (baseline) (mean±SD) (mmol/L)	138.1±2.57	138±2.83	0.28
Potassium (baseline) (mean±SD) (mmol/L)	4.44±0.54	4.11±0.34	0.0002
Chloride (baseline) (mean±SD) (mEq/L)	105.49±3.34	103.3±2.77	0.001
Ph (baseline) (mean±SD)	7.33±0.06	3.36±0.04	0.057
Bicarbonate (baseline) (mean±SD) (mmol/L)	20.81±2.82	23.66±0.78	<0.001
Copeptin (baseline) (mean±SD) (pg/ml)	483.08±319.2	440.27±179.32	0.21
NGAL (baseline) (mean±SD) (ng/ml)	13.53±11.72	1.76±2.37	<0.0001
Cystatin (baseline) (mean±SD) (ng/ml)	1512.98±643.77	719.68±106.96	<0.0001

Table 2: Comparison of copeptin, NGAL and Cystatin at baseline and 1-year follow-up in cases

Variable	At baseline	At 1 year	*P*
Copeptin (mean±SD) (pg/ml)	483.08±319.2	1046.82±823.53	<0.0001
NGAL (mean±SD) (ng/ml)	13.53±11.72	16.89±14.69	0.08
Cystatin (mean±SD) (ng/ml)	1512.98±643.77	1841.91±727.69	0.008

*NGAL=Neutrophil gelatinase-associated lipocalcin

Table 3: Change in copeptin levels during follow-up in various stages of chronic kidney disease

Stages of chronic kidney disease	Mean±SD of copeptin levels
Stage 2	−572.9088±681.1179 pg/ml
Stage 3	−523.0586±652.7129 pg/ml
Stage 4	−672.228±727.6822 pg/ml

The copeptin levels have been shown to be significantly higher in males compared to females in healthy volunteers.[14] In a study by Meijer E *et al.*,[15] the median copeptin levels were significantly higher in males than females and the high copeptin concentrations were associated with high 24-hour urinary osmolarity and low 24-hour urinary volume. However, we did not perform 24-hour urinary volume and osmolarity in our study. They also found that copeptin was associated with renal function, and those with higher copeptin levels in their study had lower renal functions, similar to ours.

The interaction between age and copeptin was significant in the older age population, with higher concentrations of copeptin found with increasing age.[10,11] As our study population consisted mainly of a younger age group, this might explain the comparable baseline copeptin levels between cases and controls in our study.

However, there was a significant increase in levels of copeptin at baseline when compared to 1-year follow-up in children with CKD. These data suggest that in children with CKD, the association between an increase in copeptin levels and a decline in renal function is likely due to decreased renal clearance. In a study in renal transplant recipients, copeptin was found to be elevated in patients with accelerated renal function decline.[16]

Biomarkers in CKD, such as cystatin C and NGAL, which are biomarkers of kidney function and CKD progression, have been extensively used in studies.[3] We also observed that cystatin C and uNGAL, markers of kidney function, were significantly increased in children with CKD compared to controls. Therefore, our study demonstrates the usefulness of copeptin as a marker of decline in kidney function.

In a study of ADPKD patients, the serum concentration of copeptin was associated with the need for kidney replacement therapy (KRT) in long-term follow-up.[5] However, we did not enrol any children with CKD stage 5; hence, our study cannot comment on the role of copeptin in KRT.

The limitation of our study was that we recruited a very small number of patients with stage 4 and above CKD. We did not detect any significant deterioration in renal function during 12 months of follow-up as most of our patients had underlying CAKUT, which is known to have a slow progression of CKD. In addition, we could not enrol age and sex-matched controls, which could have influenced the copeptin level between the cases and controls.

Conclusion

Serum copeptin levels were higher in children with progressively higher stages of CKD. However, we could not demonstrate a significant correlation between the change in eGFR and copeptin levels during 12 months of follow-up.

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Conflicts of interest

There are no conflicts of interest.

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