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EVALUATION OF SERUM PROTEINS (CTRP12 AND ADIPSIN) AS BIOMARKERS OF CHRONIC KIDNEY DISEASE AMONG INDIAN POPULATION

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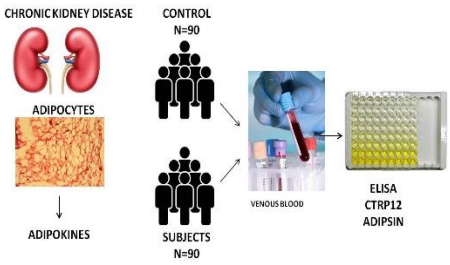
Abstract

Background: *Chronic kidney disease (CKD) is a progressive disorder marked by a gradual decline in renal function, often associated with systemic inflammation and metabolic dysregulation. Adipokines such as Adipsin and C1q/TNF-related protein 12 (CTRP12) have been implicated in metabolic and inflammatory pathways, but their roles in CKD remain underexplored.* ***Methods:*** *A case-control study was conducted involving 90 CKD patients and 90 healthy controls from the Indian population. Serum levels of CTRP12 and Adipsin were quantified using ELISA. Standard biochemical parameters, including serum creatinine, blood urea nitrogen (BUN), uric acid, calcium, C-reactive protein (CRP), and estimated glomerular filtration rate (eGFR), were measured using spectrophotometric methods. Statistical analyses included independent t-tests, Mann-Whitney U-tests, correlation analysis, and Bonferroni correction for multiple comparisons.* ***Results:*** *CKD patients exhibited significantly elevated levels of serum creatinine (7.519 ± 2.023 mg/dL), BUN (94.226 ± 19.647 mg/dL), uric acid (17.060 ± 5.848 mg/dL), and CRP (42.560 ± 15.169 mg/dL), alongside reduced eGFR (26.149 ± 6.337 mL/min/1.73 m²) and calcium levels (6.526 ± 1.058 mg/dL) compared to controls ($p < 0.001$). CTRP12 levels were significantly lower in CKD patients (0.985 ± 0.252 ng/mL) versus controls (1.390 ± 0.701 ng/mL), while Adipsin levels were significantly elevated (28.233 ± 6.532 ng/mL vs. 12.928 ± 4.612 ng/mL, $p < 0.001$). A weak but positive correlation was observed between CTRP12 and Adipsin levels ($r = 0.204$, $p = 0.046$).* ***Conclusion:*** *This study highlights significant alterations in CTRP12 and Adipsin levels among CKD patients, supporting their potential roles as supplementary biomarkers for early detection and monitoring of CKD. Further large-scale, longitudinal studies are necessary to validate these findings and explore their mechanistic roles in CKD progression.*

Keywords: *Chronic Kidney Disease, CTRP12, Adipsin, Biomarkers, Indian Population, Renal Function, Inflammation*

Graphical Abstract:



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INTRODUCTION

Chronic kidney disease (CKD) is a significant global health concern due to its association with cardiovascular events and adverse health outcomes. Affecting approximately 8% to 16% of the global population, CKD often remains asymptomatic until reaching advanced stages [Jha, V., 2013]. Although CKD is prevalent worldwide, studies report a higher incidence in low- and middle-income countries, including India, compared to high-income nations [Ene-Iordache, B., 2016]. The rising prevalence of diabetes and hypertension—the two most common risk factors for CKD—further exacerbates this trend [Redmon, J.H., 2014].

Globally, CKD prevalence ranges from 10% to 20%, with a notable increase observed in wealthier nations [Hill, N.R., 2016]. In India, the burden of CKD is expected to escalate due to factors such as an aging population and increasing rates of diabetes and hypertension [Ruiz-Ortega, M., 2020]. Furthermore, CKD patients often present with comorbidities, including obesity and diabetes, complicating diagnosis and treatment [Murton, M., 2021]. These variations highlight the complex etiology of CKD, influenced by environmental factors, comorbid conditions, and genetic predispositions [Liu, M., 2018]. Addressing these complexities is essential for improving disease management and slowing CKD progression [Duan, J., 2019].

Recent advances in molecular research have enhanced the understanding of CKD pathogenesis, leading to the discovery of novel therapeutic strategies that have improved treatment outcomes [Cañadas-Garre, M., 2019]. Nevertheless, early diagnosis remains challenging, as many individuals with CKD exhibit few or nonspecific symptoms. Monitoring renal function typically involves assessing markers such as albuminuria, serum creatinine, cystatin C, and glomerular filtration rate (GFR) [Steubl, D., 2016]. Although these markers are widely used in clinical practice, their relationship with GFR is nonlinear, and significant renal impairment may occur before substantial changes are detected. For example, serum creatinine levels often rise only after 40% to 50% of renal parenchyma is damaged [Liu, K.Z., 2020]. Therefore, early intervention is critical, and the identification of accurate and sensitive biomarkers is essential for timely diagnosis and effective management [Inker, L.A., 2016].

Given these diagnostic challenges, novel biomarkers such as adipokines have gained increasing attention. C1q/TNF-related protein 12 (CTRP12), a member of the CTRP family predominantly expressed in adipose tissue, is implicated in regulating insulin signaling, energy metabolism, and inflammation [Libby, P., 2019]. Although CTRP12 is associated with type 2 diabetes, its role in diabetic nephropathy and CKD remains unclear [Tsao, C.W., 2022]. Adiponectin, another adipokine, has been linked to CKD progression, with elevated levels observed in patients with end-stage renal disease (ESRD) [Coimbra, S., 2019]. While adiponectin is known for its anti-inflammatory and anti-atherogenic properties, its elevated levels in CKD may reflect impaired renal clearance rather than a direct causal role [Martínez Cantarin, M., 2014].

Moreover, adiponectin has been shown to inhibit the differentiation of M2 macrophages into the pro-inflammatory M1 phenotype and to suppress pro-inflammatory cytokine production, suggesting a protective role against renal inflammation [Choi, H.M., 2020]. Despite these beneficial properties, CKD patients frequently exhibit insulin resistance, systemic inflammation, and cardiovascular complications, complicating the interpretation of adiponectin's role [Achari, A.E., 2017]. Paradoxically, elevated adiponectin levels in CKD are associated with increased risk of cardiovascular disease, diabetes, and atherosclerosis, raising questions about its utility as both a biomarker and predictor of CKD progression [Song, S.H., 2020].

In light of these findings, this study aims to evaluate the relationship between serum CTRP12 and Adipsin levels in CKD patients from India. Additionally, we seek to investigate how these adipokines correlate with renal function markers, including serum creatinine, urea, uric acid, C-reactive protein (CRP), and calcium. Understanding the role of these biomarkers could contribute to the development of early detection strategies and ultimately improve patient care for CKD in the Indian population.

MATERIALS AND METHODS

Participants and Study Design

This cross-sectional study was conducted at the Department of Biochemistry and Forensic Science, Gujarat University, Gujarat, India, between December 2021 and December 2024. A total of 180 participants were recruited, comprising 90 patients diagnosed with chronic kidney disease (CKD) and 90 healthy controls.

Diagnosis and Staging

CKD diagnosis was based on elevated serum creatinine, increased blood urea nitrogen (BUN), elevated serum uric acid, and reduced estimated glomerular filtration rate (eGFR). The eGFR was calculated using the CKD-EPI formula. Staging of CKD was performed according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines. Participants with an eGFR < 60 mL/min/1.73 m² persisting for at least three months were classified as having CKD. Based on a mean GFR of 26.149 ± 6.337 mL/min/1.73 m², the majority of patients were categorized as Stage 4 CKD. The distribution across CKD stages was as follows: Stage 3 (24.4%), Stage 4 (42.2%), and Stage 5 (33.3%).

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Inclusion and Exclusion Criteria

Eligible participants were adults aged between 18 and 65 years. Inclusion criteria for the CKD group included a confirmed diagnosis of CKD as defined above. Patients with acute kidney injury, cardiovascular disease, uncontrolled hypertension, diabetic nephropathy, malignancy, or infectious diseases were excluded from the study.

The control group consisted of 90 age- and sex-matched healthy individuals recruited from the general population after comprehensive health screening. Controls demonstrated normal kidney function (eGFR > 90 mL/min/1.73 m^2) and had no history of systemic diseases such as hypertension, diabetes mellitus, cardiovascular disease, or chronic inflammatory conditions.

Baseline Characteristics

The CKD group included 55 males (61.1%) and 35 females (38.9%), with a median age of 45 years. The control group had a similar age and sex distribution (matched). Among CKD patients, comorbidities included hypertension (65%) and type 2 diabetes mellitus (48%).

The study was approved by the Institutional Ethics Committee of Gujarat University. Written informed consent was obtained from all participants prior to enrollment.

Sample Collection, Biochemical Measurements, and Statistical Analysis

Blood Sample Collection

Approximately 5 mL of venous blood was collected from each participant. Serum was separated by centrifugation and stored at −20°C until further analysis.

Biochemical Measurements

Renal Function Tests

Serum Creatinine:

Measured using a spectrophotometric method involving the oxidation of p-methylamine phenol sulfate (Metol) in the presence of copper sulfate [Avinash Krishnegowda, 2017].

Blood Urea Nitrogen (BUN):

Assessed by measuring the absorbance of the blue-green complex formed when ammonium ions react with chloride and salicylate [Koziolek & Mueller, 2020].

Serum Uric Acid:

Determined by measuring the absorbance at 700 nm of the blue-colored complex formed in the presence of phosphotungstic acid [Koziolek & Mueller, 2020].

ELISA Assays

Adipsin:

Serum Adipsin levels were measured using the Elabscience® Human CFD (Complement Factor D) ELISA Kit (Catalog No: E-EL-H6007) following the manufacturer's instructions.

CTRP12:

Serum CTRP12 levels were assessed using the Human FAM132A (Family with Sequence Similarity 132, Member A) ELISA Kit (Catalog No: ELK6599) according to the manufacturer's protocol.

ELISA Procedure

Briefly, 100 µL of standards, blanks, and serum samples were added to designated wells and incubated at 37°C for 90 minutes. After decanting the wells, 100 µL of biotinylated detection antibody was added, followed by incubation at 37°C for 60 minutes. Plates were washed three times, and 100 µL of HRP conjugate was added, followed by a 30-minute incubation. After five additional washes, 90 µL of substrate reagent was added, and plates were incubated at 37°C for 15 minutes. Finally, 50 µL of stop solution was added, and the optical density (OD) was measured at 450 nm using a microplate reader.

Statistical Analysis

Statistical analyses were performed using SPSS software (Faculty Version, IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. For normally distributed data, comparisons between CKD patients and healthy controls were conducted using independent-samples t-tests. For non-normally distributed variables, the Mann-Whitney U-test was applied. Correlations between CTRP12, Adipsin, and biochemical parameters were assessed using Pearson or Spearman correlation coefficients, depending on data distribution. Results were expressed as mean ± standard deviation (SD). A two-tailed p-value of <0.05 was considered statistically significant. Given multiple comparisons, Bonferroni correction was applied (adjusted $\alpha = 0.00625$).

Exact p-values were reported unless <0.001.

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RESULTS AND DISCUSSION

Participant Characteristics

The patient group (n=90) had a median age of 45 years (mean: 45 years), and the control group (n=90) had a median age of 45 years (mean: 46 years), with no significant age difference between the groups.

Biochemical Parameters

Serum Creatinine: Serum creatinine levels were significantly elevated in CKD patients (7.519 ± 2.023 mg/dL) compared to healthy controls (0.660 ± 0.127 mg/dL), confirming impaired renal function (Figure 1).

Blood Urea Nitrogen (BUN): BUN levels were markedly higher in CKD patients (94.226 ± 19.647 mg/dL) than in controls (31.683 ± 7.863 mg/dL), supporting the association between CKD progression and nitrogenous waste accumulation (Figure 1).

Serum Uric Acid: Serum uric acid levels were significantly elevated in CKD patients (17.060 ± 5.848 mg/dL) compared to controls (4.865 ± 0.825 mg/dL), consistent with impaired renal clearance (Figure 1).

Basic Biochemical Parameters

Serum creatinine, blood urea nitrogen (BUN), and serum uric acid levels were significantly higher in CKD patients compared to healthy controls, whereas estimated glomerular filtration rate (eGFR) and serum calcium levels were significantly lower ($p < 0.001$ for all comparisons) (Table 1).

Table 1. Comparison of basic biochemical parameters between CKD patients and controls. These findings are consistent with the typical biochemical profile of chronic kidney disease and validate the classification of the study cohort.

Parameter	CKD Patients (mean ± SD)	Controls (mean ± SD)	p-value
Creatinine (mg/dL)	4.569 ± 1.675	0.921 ± 0.239	<0.001
BUN (mg/dL)	56.233 ± 12.357	14.487 ± 4.662	<0.001
Uric Acid (mg/dL)	8.612 ± 1.245	4.209 ± 1.098	<0.001
eGFR (mL/min/1.73m²)	26.149 ± 6.337	89.675 ± 12.561	<0.001
Calcium (mg/dL)	6.526 ± 1.058	8.947 ± 0.636	<0.001

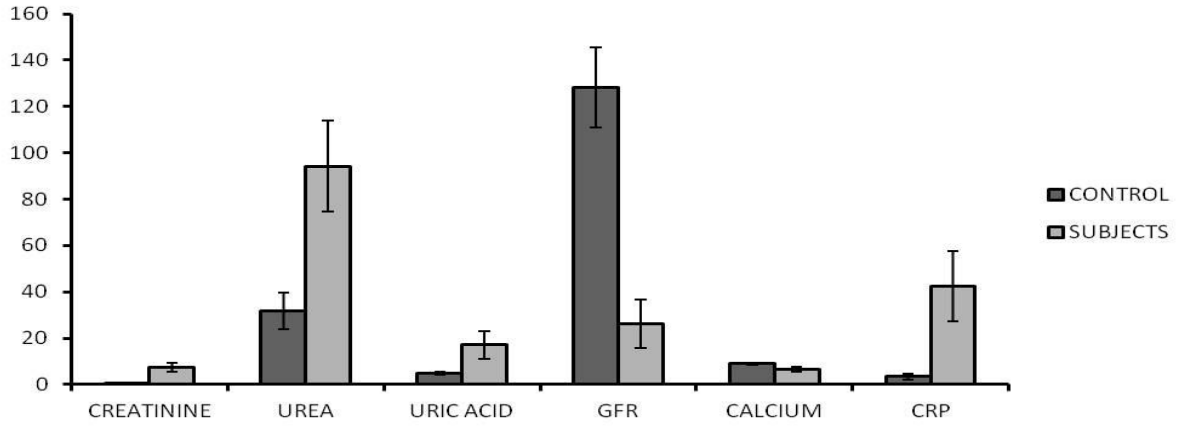

Figure 1. Bar graphs showing mean ± SD levels of serum creatinine, BUN, serum uric acid, eGFR, CRP, and calcium in CKD patients and controls. Three replicates of each experiment were conducted. $P < 0.05$.

Glomerular Filtration Rate (GFR)

The mean GFR was significantly reduced in CKD patients (26.149 ± 6.337 mL/min/1.73 m²) compared to controls (89.675 ± 12.561 mL/min/1.73 m²), confirming severe renal dysfunction among CKD patients (Figure 1).

C-Reactive Protein (CRP) and Calcium Levels

CRP: CKD patients exhibited significantly higher CRP levels (42.560 ± 15.169 mg/dL) compared to controls (3.533 ± 0.861 mg/dL), indicating heightened systemic inflammation (Figure 1).

Calcium: Serum calcium levels were significantly lower in CKD patients (6.526 ± 1.058 mg/dL) compared to controls (8.941 ± 0.594 mg/dL), aligning with the mineral and bone disorder commonly observed in CKD (Figure 1).

CTRP12 Levels

Serum CTRP12 levels were significantly lower in CKD patients (0.985 ± 0.252 ng/mL) compared to healthy controls (1.390 ± 0.701 ng/mL) (**$p < 0.001$**) (Figure 2). The effect size (Cohen's d) for CTRP12 reduction was 0.73, suggesting a moderate-to-large biological effect.

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These results suggest a strong negative association between CTRP12 levels and CKD, supporting its potential as a diagnostic biomarker.

Adipsin Levels

Conversely, serum Adipsin levels were significantly elevated in CKD patients (28.233 ± 6.532 ng/mL) compared to controls (12.928 ± 4.612 ng/mL) (**$p < 0.001$**) (Figure 3).

The effect size (Cohen's d) for Adipsin elevation was 2.76, indicating a very large biological effect. The elevated Adipsin levels in CKD patients reinforce its potential involvement in CKD pathophysiology and its utility as a biomarker.

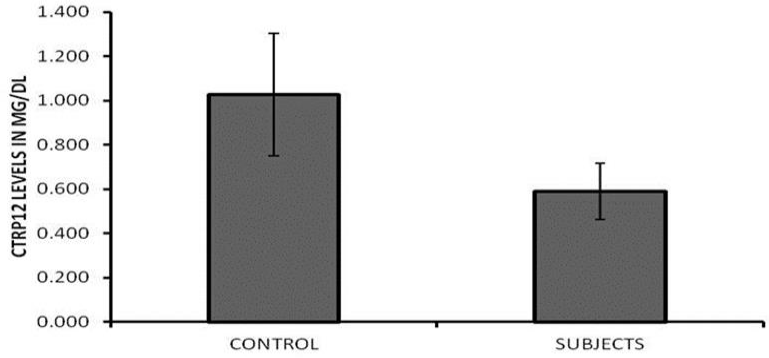


Figure 2. Bar graph showing serum CTRP12 levels in CKD patients and controls. Data represent mean ± SD; experiments were performed in triplicate. $P < 0.05$.

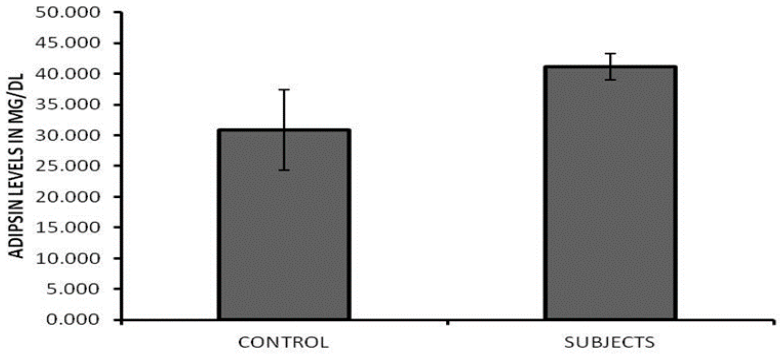
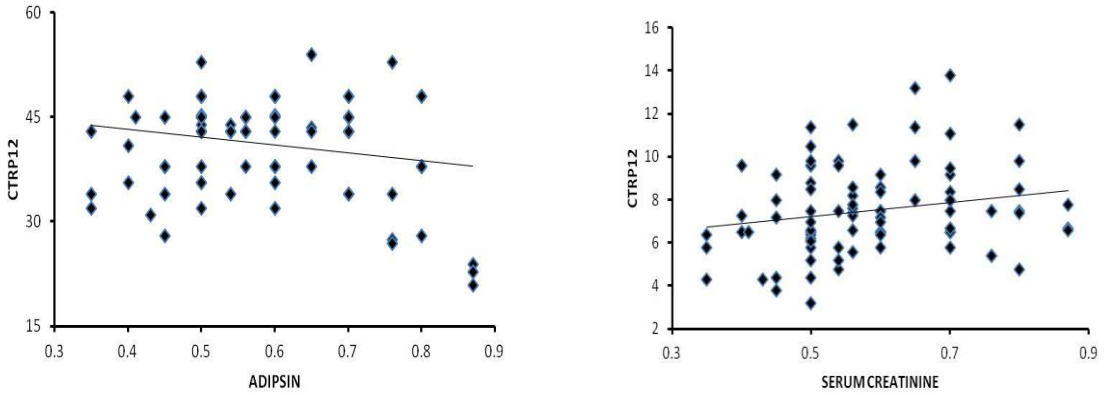


Figure 3. Bar graph showing serum Adipsin levels in CKD patients and controls. Data represent mean ± SD; experiments were performed in triplicate. $P < 0.05$.

Correlation Studies between CTRP12 and Adipsin

Linear regression analysis demonstrated a weak but positive correlation between CTRP12 and Adipsin levels ($r = 0.204$, $p = 0.046$) among CKD patients. Additionally, a positive correlation was observed between CTRP12 and serum creatinine levels ($r = 0.204$, $p = 0.045$) (Figure 4). Although statistically significant, these correlations were



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modest in strength, suggesting that while associations exist, other confounding factors may influence these relationships.

Figure 4. Correlation graphs showing the positive distribution between serum CTRP12 and serum creatinine, and between CTRP12 and Adipsin levels.

The observed decrease in CTRP12 and increase in Adipsin among CKD patients, along with their modest correlations with renal function markers, support the hypothesis that these adipokines may serve as supplementary biomarkers for early detection and monitoring of CKD progression in the Indian population.

DISCUSSION

Chronic kidney disease (CKD) is a progressive disorder characterized by a gradual decline in kidney function, often culminating in the need for renal replacement therapies such as dialysis or transplantation (Schrauben SJ, 2019). The pathophysiology of CKD is multifactorial, involving dysregulation of adipokines, which are key regulators of insulin sensitivity, adipogenesis, energy metabolism, endothelial function, and blood pressure (Farhan, Layla & Abed, 2023).

One such adipokine, C1q/TNF-related protein 12 (CTRP12), also known as adipolin, plays a critical role in regulating lipid metabolism and insulin sensitivity. Animal models of diabetes and obesity have demonstrated that CTRP12 improves glycemic control, enhances insulin sensitivity, reduces inflammation, and inhibits triglyceride synthesis in hepatocytes (Wang G., 2021).

In the present study, we observed significantly elevated levels of C-reactive protein (CRP) in CKD patients (42.560 ± 15.169 mg/dL) compared to controls, indicating a pronounced inflammatory state. Elevated CRP levels are well-established markers of systemic inflammation and have been associated with increased morbidity and mortality in CKD patients (Li J et al., 2022). Furthermore, CRP contributes to renal tissue damage, inflammation, and fibrosis, accelerating CKD progression (Li ZI, 2011; Messias BA, 2020).

Calcium levels were significantly lower in CKD patients (6.526 ± 1.058 mg/dL), consistent with the mineral and bone disorder often observed in CKD. Dysregulated calcium and phosphate metabolism contributes to vascular calcification and cardiovascular complications, common comorbidities in CKD.

Interestingly, adiponectin — another adipokine — was found to be significantly elevated in CKD patients compared to controls. A negative correlation was noted between adiponectin levels and renal function parameters such as serum creatinine and glomerular filtration rate (GFR), suggesting that elevated adiponectin may reflect kidney dysfunction (Stevens LA, 2010). Previous studies have reported similar findings, linking elevated adiponectin to insulin resistance, cardiovascular morbidity, and mortality in CKD patients (Zoccali C., 2000; Martinez Cantarin, 2013). Elevated adiponectin may represent a compensatory mechanism in response to renal impairment, although its exact role in disease progression remains to be clarified.

In contrast, CTRP12 levels were significantly reduced in CKD patients (0.985 ± 0.252 ng/mL) compared to controls. This finding aligns with previous studies showing decreased CTRP12 levels in diabetic nephropathy and CKD, suggesting a potential link between reduced CTRP12 and impaired renal function (Du J et al., 2020; Fadaei R., 2019). Given its known role in glucose and insulin metabolism, CTRP12 may also influence kidney disease progression, particularly in individuals with diabetes.

The observed negative correlations between CTRP12 and renal function markers, such as blood urea nitrogen (BUN) and serum uric acid (UA), further support the hypothesis that lower CTRP12 levels reflect more severe renal impairment. In type 2 diabetes, CTRP12 levels have been shown to correlate strongly with renal damage, making it a potential early biomarker for kidney dysfunction (Du J et al., 2020).

Although our findings provide important insights into the association between CTRP12, Adipsin, and CKD, several limitations must be acknowledged:

Cross-sectional design: The study's design limits causal inferences. While significant associations were observed, it remains unclear whether changes in CTRP12 and Adipsin levels contribute to CKD progression or are consequences of it. Longitudinal studies are needed to clarify these relationships.

Sample size: The relatively modest sample size (90 CKD patients and 90 controls) may limit the generalizability of the findings. A formal power calculation was not performed prior to study initiation, raising the possibility that the study may be underpowered to detect smaller effect sizes. Larger studies are warranted to confirm and extend these observations.

Potential confounding factors: No adjustments were made for confounding variables such as diabetes mellitus and hypertension, both of which are highly prevalent in CKD and can independently influence CTRP12 and Adipsin levels.

Future studies incorporating multivariable regression analyses are necessary to address these confounders.

Finally, the observed elevations in serum creatinine, BUN, and the reduction in GFR were consistent with the established biochemical profile of CKD, reinforcing the internal validity of the study cohort.

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CONCLUSION

In this study, we demonstrated significant alterations in CTRP12 and Adipsin levels among CKD patients in the Indian population, suggesting their potential as early biomarkers for disease detection and monitoring. Decreased CTRP12 levels and elevated Adipsin levels were strongly associated with impaired renal function. Although the findings support a possible role for these adipokines in CKD pathophysiology, further large-scale, longitudinal studies are required to validate these associations and clarify their clinical utility in early diagnosis and prognosis of CKD.

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ETHICS CLEARANCE AND PARTICIPATION CONSENT

This work was approved by Institutional Ethics Committee (IEC), Gujarat University, Ref No. : GU-IEC (NIV)/06/PhD/076. The research work was carried out in compliance with all applicable rules and laws.

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