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Research Article

ASSESSMENT OF SERUM CTRP12 AND ADIPSIN AS POTENTIAL BIOMARKERS FOR CHRONIC KIDNEY DISEASE IN THE IRAQI POPULATION

MOHAMMED M ABDULKADHM[1], AWS RASSUL HUSSAIN[2], RAKESH M. RAWAL[1], RUSHIKESH JOSHI[1]*

[1]Department of Biochemistry and Forensic Science, University School of Sciences, Gujarat University, Ahmedabad, Gujarat, India.
[2]Department of Pathology, College of Medicine, University of Al-Qadisiyah, College of Medicine Department of Pathology, Diwaniyah, Iraq.
*Corresponding author: Rushikesh Joshi, Email: rushikeshjoshi@gujaratuniversity.ac.in

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ABSTRACT

Objective: The blood levels of Cystatin C and creatinine, as well as glomerular filtration rate (GFR), in clinical practice to assess impaired kidney function, particularly the existence of albuminuria. Although they are often employed, estimates of GFR mentioned above are not exact. As a result, early-stage chronic kidney disease (CKD) may continue to be undiagnosed. It is crucial to emphasize that early CKD treatment can either improve kidney function or, at the very least, halt the disease's progression. In our study, we wish to find at the levels of serum Adipsin and C1q/Tumor Necrosis Factor -related protein-12 (CTRP12) among the CKD subjects from the Iraqi population.

Methods: We estimated serum Adipsin and CTRP12 levels using the ElabScience Enzyme-Linked Immunosorbent Assay kits. Along with these protein levels, we tried to find the possible correlation between several blood markers and chronic renal disease in the subjects.

Results: When compared to controls, the individuals' serum creatinine, blood urea, uric acid in serum, and CRP levels were discovered to be greater ($p<0.01$). The glomerular filtration rate and it was discovered that the sufferers' group had lower calcium levels than the group with control ($p<0.01$). CTRP12 was discovered to be reduced, whereas it was discovered that Adipsin was higher than the control ($p<0.01$). From multiple correlation studies, we found that Adipsin and CTRP12 presented a positive relation ($r=0.164129$), and CRP with CTRP12 showed a positive relation ($r=0.160291$).

Conclusion: From this, we can conclude that serum levels of CTRP12 and Adipsin should be used as novel markers to detect CKD in both early and disease progression stages.

Keywords: Chronic kidney disease, Adipsin, C1q/tumor necrosis factor-related protein-12, Receiver operating characteristic curve, Enzyme-linked immunosorbent assay.

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INTRODUCTION

Around the globe, chronic kidney disease (CKD) is now at the 16th position in causing mortality. To avoid any unwanted CKD-related outcomes, such as heart disease or kidney disease, physicians need to do appropriate screening, diagnosis, and treatment [1]. Even though kidney disease can be prevented in large part by early identification, its development, and associated problems, numerous studies show that the general public is not well-informed about renal diseases. Thus, enhancing knowledge and putting long-term solutions for kidney disease early detection into practice are among the goals of public health. Data from epidemiology and economics highlight the need to include renal illness on the agenda for global public health because its incidence is rising, and it is currently the ninth most common risk factor for death globally. Furthermore, it is anticipated that the obesity pandemic, demographic shifts, and climate change's effects will all lead to a rise in the incidence of kidney illness. Globally, this will have a major effect on healthcare spending, survival and quality of life [2].

<60 mL/min/1.73 square meters of estimated glomerular filtration rate (eGFR) and the ongoing existence of kidney damage signs and markers of kidney illness that is chronic (CKD), a steady decline in kidney function, is indicated by the existence of proteinuria, structural irregularities, histological damage, active urine sediments, or kidney transplant history spanning longer than 3 months, or both [3]. CKD has long been a huge financial burden and a global health concern and medical burden because it is known that a lower GFR raises the risk of cardiac injury, hospitalization as well as total death rates [4]. Geographically, the prevalence of CKD varies, typically falling between 10 and 20%, but it gradually increases, especially in developed nations [5]. The growing aging of the world's population is partly to blame for this tendency. Furthermore, it is noteworthy that patients with risk factors including diabetes mellitus (DM), obesity, and high blood pressure are more prevalent in people with CKD or chronic renal disease.

After a person's renal function has reached a "point of no return," they are diagnosed with CKD, meaning that gradual decline in renal function is unavoidable and often permanent. Nonetheless, patients with CKD may still exhibit various patterns of deterioration in renal function [6]. Due to the diverse character of CKD and a lack of knowledge about its detrimental effects, managing patients with this condition is difficult and complex [7]. Early medical management for consequences, including anemia and prompt identification of AKI, ketoanalogs, low-protein diet, and metabolic acidosis, io delay the progression of renal disease and reduce the morbidity and mortality of CKD patients, hyperkalemia and CKD-mineral bone disorder are essential., along with modifying lifestyle choices and addressing risk factors for CKD [8].

Because of the advancements made in our comprehension of the basic pathways behind the illness, the continuous development of new therapeutic medications, and the implementation of these discoveries from the lab to the bedside, it is anticipated that the efficacy of CKD treatments will rise [9].

It is challenging to diagnose these patients in a timely manner because many of them are asymptomatic or have vague symptoms. Since any component of the nephron can be affected by kidney illnesses, which are varied and complex, when assessing renal function clinically, the glomerulus is crucial [10]. In clinical practice, the presence of albuminuria, values of GFR, creatinine, and cystatin C in serum are used to indicate compromised kidney function. Although imperfect, estimates of GFR based on the aforementioned indicators are frequently utilized. Creatinine/cystatin C and they have a nonlinear relationship [11]. Because creatinine/cystatin C and GFR have a nonlinear relationship, relatively minor beginning increases in these indicators correspond to large GFR declines. Only when 40–50% of the renal parenchyma is destroyed does the serum creatinine concentration rise [12]. It is crucial to emphasize that early CKD treatment can either improve kidney function or, at the very least, halt the disease's progression. Kidney function indicators in the blood and urine are being utilized more and more to identify CKD early on, provide the right treatment, and enhance patient care and prognosis [13].

Because of the advancements made in our comprehension of the basic pathways behind the illness, the continuous development of new therapeutic medications, and the implementation of these discoveries from the lab to the patient's bedside, it is anticipated that the efficacy of CKD treatments will rise [9]. Among the recently investigated families of adipokines, type 2 diabetes is believed to be associated with C1q/tumor necrosis factor-related protein-12 (CTRP12) in serum. Nevertheless, it is still unknown how the relationship between serum CTRP12 levels and diabetic nephropathy [14]. The paralogs of adiponectin (ADP) belonging to the family of CTRP, which comprises CTRP1 through CTRP15, are most highly expressed in the surrounding adipose tissue of the heart [15]. The evidence is mounting that the CTRP family is involved in energy metabolism, insulin signaling, inflammatory regulation, and the cardiovascular system. The role of members of the CTRP family as ACS biomarkers that predict is presently uncertain because of their danger of in various ACS subgroups is still unknown [16,17].

Hence, this study's objective was to look into the connection between CKD patients' serum CTRP12 and Adipsin levels. In addition, we looked at the relationship between renal function test indicators and CTRP12 and Adipsin (urea, creatinine, serum albumin), calcium, and phosphorus among the subjects.

METHODS

Study population

The Department of Biochemistry Laboratory at Al-Diwaniyah Teaching Hospital in Diwaniyah, Iraq, conducted this case-control study between December 2021 and June 2024. A total of 180 (n=180) samples they had been divided up separated into two categories: Group 1 includes 90 patients diagnosed with CKD, and Group 2 includes 90 normal individuals as a control.

Inclusion criteria

All adult patients were diagnosed with CKD. Elevated blood urea and serum creatinine levels served as the primary basis in order to identify CKD, which states kidney CKD is accompanied by viral load beyond the reference range. X-rays or CT scans help to identify the CKD.

Exclusion criteria

Patients with diabetic nephropathy, acute kidney injury, those with cardiovascular disease, and uncontrolled hypertension were all excluded from the study.

The project received ethical permission from Gujarat University's Ethical Committee (GU-IEC (NIV)/06/PhD/076).

Blood samples

About 5 mL of blood was collected from each subject. The latter underwent centrifugation, where the serum was obtained and preserved at −20°C until used.

Biochemical tests

The spectrophotometric method was used to quantify serum creatinine, BUN, blood urea nitrogen, and uric acid (UA) in the serum. Creatinine in serum was estimated by oxidation of P-methylamine phenol sulfate when copper sulfate is present as per the protocol mentioned [18]. BUN was estimated by measuring the absorbance of the blue-green complex formed by Ammonium ions, then formed with chloride and salicylate [19]. Serum UA concentration was estimated by measuring the absorbance (700 nm) of the blue-colored complex formed in the presence of phosphotungstic acid [20].

Enzyme-linked immunosorbent assay (ELISA)

Elabscience® Human AD (Adropin) ELISA Kit (Catalog No: E-EL-H6007) was used to measure Adipsin, and Human FAM132A ELISA Kit (Cat: ELK6599) (Family With Sequence Similarity 132, Member A) was used to measure CTRP12. The protocol was followed as described in the kit. About 100 µL of different sample, blank, and standard dilutions were put into the corresponding wells. After that, the contents were incubated for about 90 min at 37°C. Following incubation, the liquid was decanted from each well and added with 100 µL of Biotinylated Detection Ab working solution. The plate was incubated at 37°C for 1 h. The contents were then decanted from each well and washed with 350 µL of buffer. Following washing, each well received roughly 100 µL of HRP Conjugate working solution, which was then incubated for about 30 min at 37°C. Following incubation, the contents were decanted from each well and washed 5 times with wash buffer. Finally, each well received 90 µL of the substrate reagent, and it was after that 15 min of incubation at 37°C. 50 µL of stop solution was added to that reaction to stop it. The plate was recorded for the optical density (OD value) with a micro-plate reader at 450nm.

Statistical analysis

The mean ± standard deviation was used to depict the data. The sample was compared between the control and participants using a one-way analysis of variance. The information was considered significant at $p<0.01$. A statistical package for the social sciences was used for the analysis (Faculty version). In an assessment that is not parametric, the coefficient of Spearman's rank was used to determine the importance of correlation for the relationship between the two numerical variables. The Adipsin cut-off value was established using the receiver operating characteristic (ROC) curve analysis.

RESULTS

The subjects' average age (n=90) was 44.44, whose median age was 42.5. The average age of the control groups (n=90) was 46.57, with a median age of 45.

Blood parameters

The serum creatinine levels were found to be significantly elevated among the patients (7.90±2.411) compared to the control (0.54±0.221). This can probably confirm the relation between CKD and creatinine levels (Fig. 1). The blood urea levels were found to be significantly elevated among the patients (30.760±8.633) when compared to the control (92±22.70). This can probably confirm the relation between the blood urea and creatinine levels (Fig. 2).

Levels of S. UA

Serum UA levels of the patients were found to be noticeably higher (12.85±4.36997) compared to the control (4.63977±0.971187). This can probably confirm the correlation between serum UA levels and CKD (Fig. 3).

GFR

The GFR was measured in mL/min/1.73 m^2. It was significantly lower among the patients (8.94±3.629966) compared to the control (119.778±25.80644). This can probably confirm the relation between CKD and GFR (Fig. 4).

CRP and calcium levels

CRP levels were measured in mg/dL. The CRP was significantly elevated among the patients group (41.82±25.074) when compared to

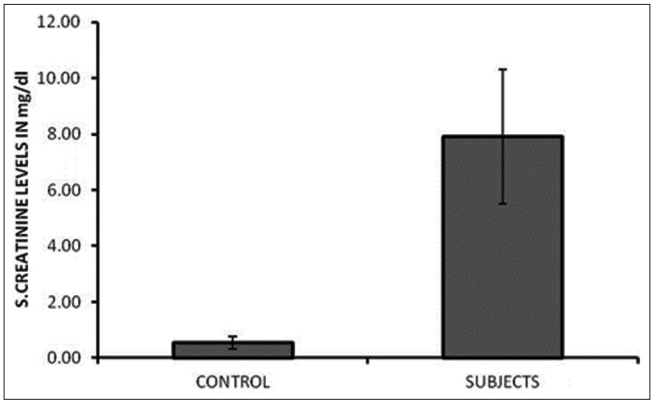

Fig. 1: Histogram drawn for the serum creatinine levels observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

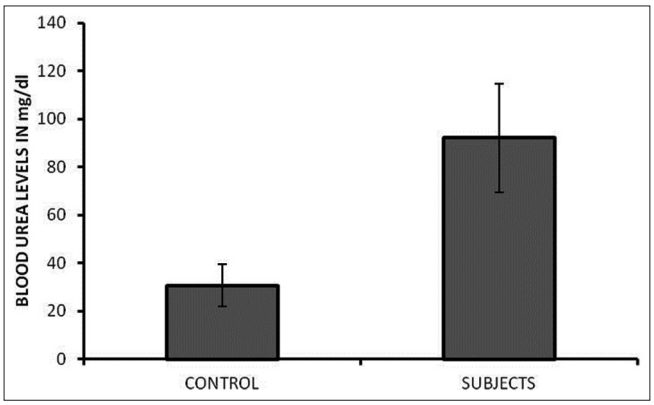

Fig. 2: Histogram drawn for the Blood urea levels observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

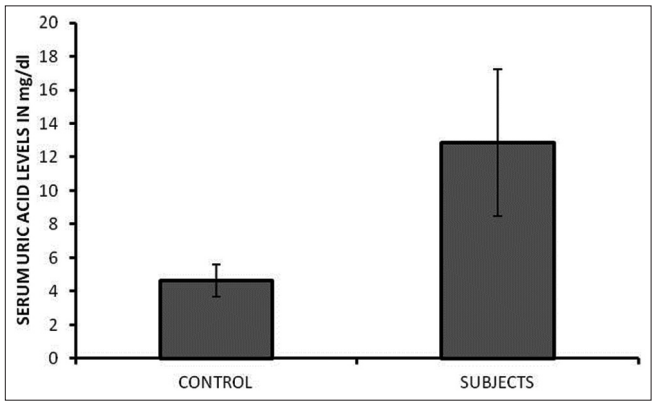

Fig. 3: Histogram drawn for the serum uric acid amounts observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

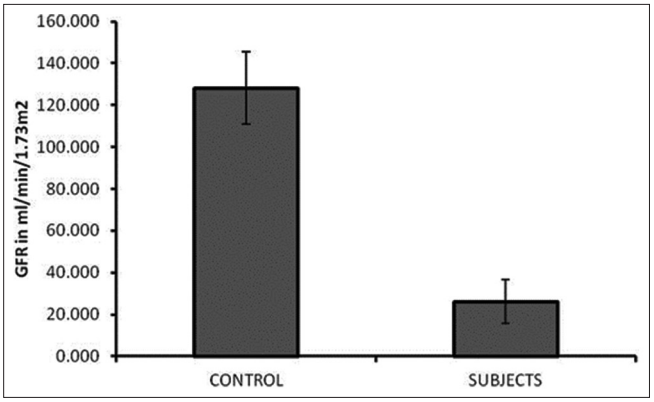

Fig. 4: Histogram drawn for the GFR observed for the subjects and control. Experiments are done in triplicates and expressed in standard deviation (p<0.05)

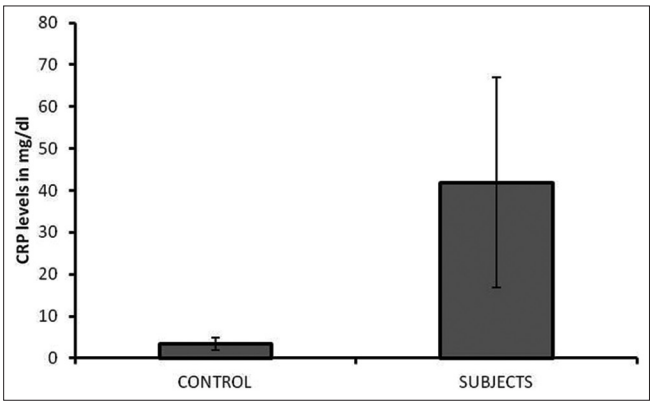

Fig. 5: Histogram drawn for the CRP observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

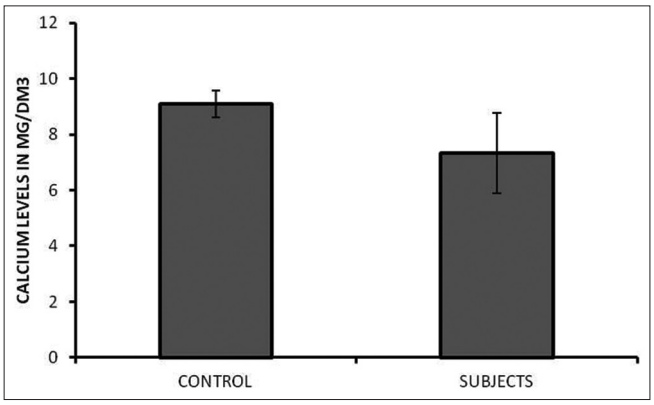

Fig. 6: Histogram drawn for the calcium levels observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

the control (3.41733±1.426) (Fig. 5). On the other hand, the calcium levels were found to be lowered among the patients group (7.33±0.487) when compared to the control (9.091±0.487) (Fig. 6). This can probably confirm the significant relation between CKD and CRP and calcium levels.

Detection of Adipsin and CTRP12

Both serum Adipsin and CTRP12 were determined by following the manufacturer's recommendations with an ELISA kit (Elabscience, USA). Human Adipsin, biotinylated detection antibody were used from the kit as secondary antibodies. The OD was checked at 452nm following incubation in an ELSIA plate reader (Biotest, Germany). We found significant results among the CTRP12 levels as determined by the ELISA method. The CTRP12 levels were found to be lowered among the patients group (0.68544±0.07042) when compared to the control (0.98511±0.2516) (Fig. 7). This would confirm the strong association between CTRP12 and CKD. The concentration of the CTRP12 for the samples was calculated using the regression equation ($y=0.021x+0.0915$; $R^2=0.9911$).

On the contrary, Adipsin levels were elevated among the subjects. The concentration of the samples was calculated using the regression equation (y=0.0217x+0.1254; R^2=0.9918). We found significant results among the Adipsin levels as determined by the ELISA method. The Adipsin level was found to be elevated among the patient group (28.233±6.53227) when compared to the control (12.9278±4.6119) (Fig. 8). This would confirm the strong association between Adipsin and CKD.

Correlation studies

Multiple linear regression analysis revealed weak correlations between the blood parameters and CTRP12 and Adipsin. Potential correlations between the two proteins and the blood parameters among the patient group were evaluated to examine the relationship between CKD protein indicators and serum markers.

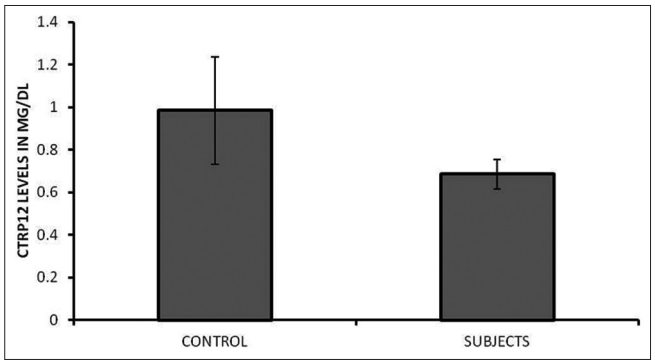

Fig. 7: Histogram drawn for the CTRP12 observed for the subjects and control. Experiments are done in triplicates and expressed in terms of standard deviation (p<0.05)

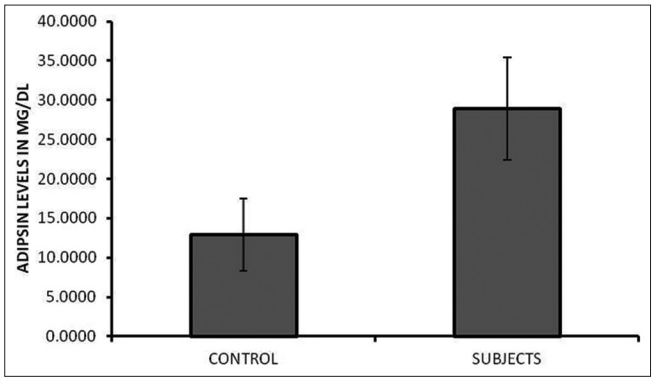

Fig. 8: Histogram drawn for the Adipsin observed for the subjects and control. Experiments are done in triplicates and expressed in standard deviation (p<0.05)

Association with CTRP12

Though there was no very strong correlation, Adipsin and CTRP12 shown a positive relation (r=0.164129), and CRP with CTRP12 shown a positive relation (r=0.160291) (Fig. 9).

Association with adipsin

There was no correlation observed between the blood parameters and Adipsin. Adipsin showed a positive correlation with CTRP12 (r=0.164129).

ROC curve analysis

At the optimal level of accurate CKD prediction, the AUC of the receiver's operational characteristic curve, which shows that chronic renal disease has been diagnosed, was 0.9927 for Adipsin and 0.9939 for CTRP12 (p<0.01). The ROC curve's area under the curve (AUC) is 0.9939 (Fig. 10). It implies that the model's ability to differentiate between two outcomes is exceptional. The better the model, the larger the AUC. When the 2.7 exceeds the threshold, the model selects 1. AUC, or the ROC curve's area under the curve, is 0.9927. It implies that the model's ability to differentiate between two outcomes is exceptional. The better the model, the larger the AUC. When the 10.5 exceeds the threshold, the model selects 1.

DISCUSSION

Kidney damage or an estimated eGFR of <60 mL/min/1.73 m^2 that lasts for 3 months or longer are signs of CKD. A steady decline in kidney function is the hallmark of CKD, which frequently calls for renal replacement therapy, such as dialysis or transplantation [20]. Numerous processes, including sensitivity to insulin, adipogenesis, insulin synthesis, energy metabolism in tissues that are susceptible to insulin, role of endothelium and blood pressure, hemostasis, activity involving energy expenditure, satiety, and appetite, are influenced by adipokines [21].

The hormone CTRP12, commonly referred to as adipolin, aids in controlling lipid metabolism and insulin sensitivity. Diabetes and obesity models in mice, CTRP12 enhances glycemic control and insulin sensitivity. Along with inhibiting the inflammatory response and encouraging efflux of cholesterol, CTRP12 prevents triglyceride production and export in hepatocytes [22].

Compared to the control, the CRP was considerably higher in the patient group (41.82±25.074). However, compared to control, the calcium levels in the subjects were lower (7.33±0.487). CKD relates to C-reactive protein (CRP), a blood test that can show inflammation. People with CKD who are more likely to pass away are associated with elevated CRP levels [23]. When infection or inflammation is severe, within 4–10 h of inflammatory activation, CRP can be produced, having a short 19-h half-life and peaking 48 h later [24]. On the other hand, chronic inflammation has been connected to chronically high CRP levels in those having CKD or end-stage renal disease [25]. Therefore, it is believed that a greater CRP level is a biomarker for inflammation, tissue damage, and the long-term emergence of diseases.

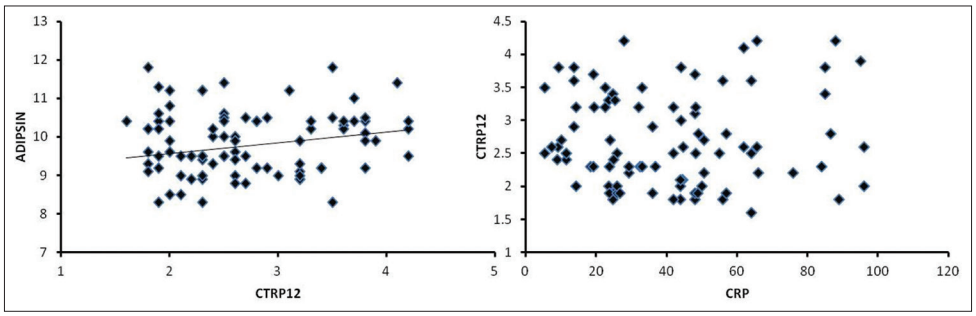

Fig. 9: Correlation graph depicting the positive correlation distribution between the CTRP12 and CRP and adipsin

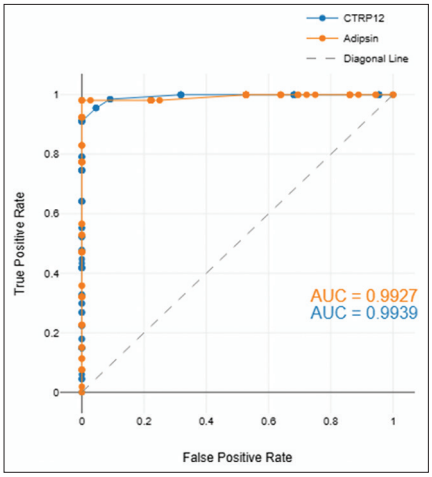

Fig. 10: Adipsin and CTRP12 levels in CKD patients are screened for predictive value using ROC curve analysis. (n=90) versus healthy patients (n=90), p≤0.01

In people with CKD in stages three and four, a high CRP level its a separate risk factor for deaths from all causes and a predictor of cardiovascular events [26]. It is well known that increased blood CRP levels are related to CKD mortality and morbidity, noting that one risk factor for CKD is CRP [27].

Information from a sizable population survey have been shown that in Africans, CKD is linked to the CRP single nucleotide polymorphism (SNP) rs2808630, Hypertension-related renal disease in non-Hispanic Black Americans [28], and that Rs2808630, a CRP SNP, is linked to albuminuria., a significant CKD risk factor development [29]. A UUO mouse model demonstrates how CRP contributes to the pathophysiology of CKD. Whereby mice with elevated levels of acute inflammation and renal fibrosis are present in human CRP.

CKD patients had considerably greater amounts of ADP compared to the group of control ($p<0.05$), and in patients of CKD, ADP had an inverse relationship with both creatinine ($p<0.01$) and rate of GFR ($p<0.001$) [30]. ADP also had an inverse relationship with GFR ($p<0.001$), according to another study [31]. Research on Iraqi individuals with CKD has revealed that Adipsin levels, a component of ADP, are frequently higher than those of healthy people. This means that CKD patients in Iraq typically have higher blood levels of Adipsin, which is consistent with findings in other populations where CKD patients typically exhibit higher levels of ADP [32]. CKD is a distinct disorder that is paradoxically linked to higher plasma ADP and has an exceptionally increased prevalence of insulin resistance in addition to cardiovascular morbidity and death [33]. The amount of plasma ADP is influenced by kidney function and is significantly higher in patients with renal impairment [34]. Kir HM *et al.* [35] in their studies stated that compared to the subjects in the dialysis group, the pre-dialysis groups' mean ADP levels were noticeably lower ($p<0.05$). Every patient with chronic renal failure (CRF) had elevated ADP levels [35,36]. In hemodialysis patients, the ADP plasma levels were significantly greater than those with CKD [37]. ADP alterations were substantially associated with changes in eGFR in CKD patients ($p=0.001$), as found by Toyama *et al*. CRF patients' plasma levels of ADP were not less than those of controls ($p=0.78$), even though 60% of CKD patients have CAD, according to another study [38].

Comparing the control group to the patients' CTRP12 levels have been shown to be lower (0.98511±0.2516) Du *et al*., [39] stated that, in people who have type 2 diabetes, decreased CTRP12 blood levels are associated with kidney failure. The hormone CTRP12 aids in the metabolism of insulin and glucose. The severity of renal insufficiency was linked to the serum CTRP12 level, which was noticeably less in the T2DM-DN group than the T2DM group and significantly less than the T2DM-DN group compared to the group of control [39] also stated that lower CTRP12 levels are linked to more severe renal insufficiency in individuals with type 2 diabetes; CTRP12 levels are negatively correlated with BUN, UA, 24-h urinary albumin excretion rate (UAE), and the duration of diabetes [40].

Serum CTRP12 levels in type 2 DM are substantially associated with renal impairment, per logistic regression analysis [41,42]. Studies have demonstrated a significant decrease in CTRP12 levels in patients with diabetic nephropathy, suggesting a potential link between reduced CTRP12 and impaired kidney function [43,44]. Low blood levels of CTRP12 have been linked in research on a higher risk of kidney damage, especially in individuals with type 2 diabetes. However, to completely comprehend the mechanisms at work, more investigation is needed [45].

CONCLUSION

Long-term kidney damage that impairs the kidneys' ability to filter blood is referred to as chronic renal disease. Anemia, elevated blood pressure, heart disease, and other health issues can all be brought on by CKD. A significant and grave worldwide health issue, CKD causes kidney impairment in addition to several systemic illnesses. Early diagnosis and therapy are two important steps to stop further decline in kidney function and postpone negative consequences. However, our capacity to quickly identify and deal with this prevalent clinical problem, which impacts >10% of the world's population, has been undermined by the lack of early, predictive, and non-invasive biomarkers. Serum creatinine and albuminuria are still used to quantify kidney function although all these restrictions and several formulas are still used to determine the eGFR.

Given that CKD in the early phases typically exhibits no symptoms, finding markers is essential for early detection of kidney damage, prompt intervention, and management of the disease before a significant decline in kidney function occurs. This could improve patient outcomes by facilitating timely treatment and tracking the progression of the disease. The most sensitive and specific marker for diagnosing diabetic patients with neuropathy is Adipsin. The course of chronic renal disease can impact adipsin levels. In T2DM with neuropathy, reduced insulin sensitivity may lead to elevated Adipsin levels. There was a favorable correlation between IR and Adipsin levels. This could imply that the Adipsin level may have an impact on the diagnosis of CKD.

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ETHICS CLEARANCE AND PARTICIPATION CONSENT

This work was approved by the Institutional Ethics Committee (IEC), Gujarat University Ref. Letter No.: (GU-IEC (NIV)/06/PhD/076) dated on June 26, 2021. Every research work was carried out in compliance with all applicable rules and laws.

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A CONFLICT OF INTEREST

No conflicts of interest have been declared.

REFERENCES

1. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: A review. JAMA. 2019 Oct 1;322(13):1294-304.

doi: 10.1001/jama.2019.14745, PMID 31573641, PMCID PMC7015670
2. Francis A, Harhay MN, Ong AC, Tummalapalli SL, Ortiz A, Fogo AB, *et al*. Chronic kidney disease and the global public health agenda: An international consensus. Nat Rev Nephrol. 2024;20(7):473-85. doi: 10.1038/s41581-024-00820-6, PMID 38570631
3. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, *et al*. Global prevalence of chronic kidney disease-A systematic review and meta-analysis. PLOS One. 2016;11(7):e0158765. doi: 10.1371/journal.pone.0158765, PMID 27383068
4. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16(5):269-88. doi: 10.1038/s41581-019-0248-y, PMID 32060481
5. Liu M, Liu SW, Wang LJ, Bai YM, Zeng XY, Guo HB, *et al*. Burden of diabetes, hyperglycaemia in China from to 2016: findings from the 1990 to 2016, global burden of disease study. Diabetes Metab. 2019;45(3):286-93. doi: 10.1016/j.diabet.2018.08.008, PMID 30196138
6. Duan J, Wang C, Liu D, Qiao Y, Pan S, Jiang D, *et al*. Prevalence and risk factors of chronic kidney disease and diabetic kidney disease in Chinese rural residents: A cross-sectional survey. Sci Rep. 2019;9(1):10408. doi: 10.1038/s41598-019-46857-7, PMID 31320683
7. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, *et al*. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59(4):504-12. doi: 10.1053/j.ajkd.2011.12.009, PMID 22284441
8. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Investig. 2006;116(2):288-96. doi: 10.1172/JCI27699, PMID 16453013
9. Cañadas-Garre M, Anderson K, Cappa R, Skelly R, Smyth LJ, McKnight AJ, *et al*. Genetic susceptibility to chronic kidney disease-some more pieces for the heritability puzzle. Front Genet. 2019;10:453. doi: 10.3389/fgene.2019.00453, PMID 31214239
10. Pasala S, Carmody JB. How to use serum creatinine, cystatin C and GFR. Arch Dis Child Educ Pract Ed. 2017;102(1):37-43. doi: 10.1136/archdischild-2016-311062, PMID 27647862
11. Steubl D, Block M, Herbst V, Nockher WA, Schlumberger W, Satanovskij R, *et al*. Plasma uromodulin correlates with kidney function and identifies early stages in chronic kidney disease patients. Medicine. 2016;95(10):e3011. doi: 10.1097/MD.0000000000003011, PMID 26962815
12. Liu KZ, Tian G, Ko AC, Geissler M, Brassard D, Veres T. Detection of renal biomarkers in chronic kidney disease using microfluidics: Progress, challenges and opportunities. Biomed Microdevices. 2020;22(2):29. doi: 10.1007/s10544-020-00484-6, PMID 32318839
13. Inker LA, Tighiouart H, Coresh J, Foster MC, Anderson AH, Beck GJ, *et al*. GFR estimation using β-trace protein and β2-microglobulin in CKD. Am J Kidney Dis. 2016;67(1):40-8. doi: 10.1053/j.ajkd.2015.07.025, PMID 26362696
14. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, *et al*. Heart disease and stroke statistics-2022 update: A report from the American Heart Association. Circulation. 2022;145(8):e153-639. doi: 10.1161/CIR.0000000000001052, PMID 35078371
15. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, *et al*. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56. doi: 10.1038/s41572-019-0106-z, PMID 31420554
16. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol. 2022;19(9):593-606. doi: 10.1038/s41569-022-00679-9, PMID 35296869
17. Si Y, Fan W, Sun L. A Review of the relationship between CTRP family and coronary artery disease. Curr Atheroscler Rep. 2020;22(6):22. doi: 10.1007/s11883-020-00840-0, PMID 32468164
18. Krishnegowda A, Padmarajaiah N, Anantharaman S, Honnur K. Spectrophotometric assay of creatinine in human serum sample. Arab J Chem. 2017;10:S2018-24. doi: 10.1016/j.arabjc.2013.07.030
19. Koziolek M, Mueller GA, Dihazi GH, Jung K, Altubar C, Wallbach M, *et al*. Urine E-cadherin: A marker for early detection of kidney injury in diabetic patients. J Clin Med. 2020;9(3):639. doi: 10.3390/jcm9030639, PMID 32121033
20. Schrauben SJ, Jepson C, Hsu JY, Wilson FP, Zhang X, Lash JP, *et al*. Insulin resistance and chronic kidney disease progression, cardiovascular events, and death: Findings from the chronic renal insufficiency cohort study. BMC Nephrol. 2019 Feb 20;20(1):60. doi: 10.1186/s12882-019-1220-6, PMID 30786864
21. Farhan LO, Abed BA, Dawood A. Comparison study between adipsin levels in sera of Iraqi patients with diabetes and neuropathy. Baghdad Sci J. 2023;20(3):23. doi: 10.21123/bsj.2022.7408
22. Wang G, Chen JJ, Deng WY, Ren K, Yin SH, Yu XH. CTRP12 ameliorates atherosclerosis by promoting cholesterol efflux and inhibiting inflammatory response via the miR-155-5p/LXRα pathway. Cell Death Dis. 2021;12(3):254. doi: 10.1038/s41419-021-03544-8, PMID 33692340
23. Li J, Chen J, Lan HY, Tang Y. Role of C-reactive protein in kidney diseases. Kidney Dis (Basel). 2023;9(2):73-81. doi: 10.1159/000528693, PMID 37065607, PMCID PMC10090978
24. Messias BA, Botelho RV, Saad SS, Mocchetti ER, Turke KC, Waisberg J. Serum C-reactive protein is a useful marker to exclude anastomotic leakage after colorectal surgery. Sci Rep. 2020 Feb 3;10(1):1687. doi: 10.1038/s41598-020-58780-3, PMID 32015374
25. O'Flynn J, van der Pol P, Dixon KO, Prohászka Z, Daha MR, van Kooten C. Monomeric C-reactive protein inhibits renal cell-directed complement activation mediated by properdin. Am J Physiol Ren Physiol. 2016 Jun 1;310(11):F1308-16. doi: 10.1152/ajprenal.00645.2014, PMID 26984957
26. Soriano S, González L, Martín-Malo A, Rodríguez M, Aljama P. C-reactive protein and low albumin are predictors of morbidity and cardiovascular events in chronic kidney disease (CKD) 3-5 patients. Clin Nephrol. 2007 Jun;67(6):352-7. doi: 10.5414/cnp67352, PMID 17598370
27. Gao J, Wang A, Li X, Li J, Zhao H, Zhang J, *et al*. The cumulative exposure to high-sensitivity C-reactive protein predicts the risk of chronic kidney diseases. Kidney Blood Press Res. 2020;45(1):84-94. doi: 10.1159/000504251, PMID 31794962
28. Hung AM, Ikizler TA, Griffin MR, Glenn K, Greevy RA, Grijalva CG, *et al*. CRP polymorphisms and chronic kidney disease in the third national health and nutrition examination survey. BMC Med Genet. 2011 May 11;12:65. doi: 10.1186/1471-2350-12-65, PMID 21569369
29. Li ZI, Chung AC, Zhou L, Huang XR, Liu F, Fu P, *et al*. C-reactive protein promotes acute renal inflammation and fibrosis in unilateral ureteral obstructive nephropathy in mice. Lab Invest. 2011 Jun;91(6):837-51. doi: 10.1038/labinvest.2011.42, PMID 21383672
30. Sedighi O, Abediankenari S. Relationship between plasma adiponectin level with inflammatory and metabolic markers in patients with chronic kidney disease. Nephrourol Mon. 2014;6(1):e11743. doi: 10.5812/numonthly.11743, PMID 24719803
31. Kamimura MA, Canziani ME, Sanches FR, Velludo CM, Carrero JJ, Bazanelli AP, *et al*. Variations in adiponectin levels in patients with chronic kidney disease: A prospective study of 12 months. J Bras Nefrol. 2012;34(3):259-65. doi: 10.5935/0101-2800.20120007, PMID 23099831
32. Heidari M, Nasri P, Nasri H. Adiponectin and chronic kidney disease; a review on recent findings. J Nephropharmacol. 2015 Jul 27;4(2):63-8. PMID 28197480, PMCID PMC5297487
33. Zoccali C. Cardiovascular risk in uraemic patients-is it fully explained by classical risk factors? Nephrol Dial Transplant. 2000;15(4):454-7. doi: 10.1093/ndt/15.4.454, PMID 10727537
34. Martinez Cantarin MP, Waldman SA, Doria C, Frank AM, Maley WR, Ramirez CB, *et al*. The adipose tissue production of adiponectin is increased in end-stage renal disease. Kidney Int. 2013;83(3):487-94. doi: 10.1038/ki.2012.421, PMID 23283133
35. Kir HM, Eraldemir C, Dervisoglu E, Caglayan C, Kalender B. Effects of chronic kidney disease and type of dialysis on serum levels of adiponectin, TNF-alpha and high sensitive C-reactive protein. Clin Lab. 2012;58(5-6):495-500. PMID 22783580
36. Elshamaa MF, Sabry SM, El-Sonbaty MM, Elghoroury EA, Emara N, Raafat M, *et al*. Adiponectin: An adipocyte-derived hormone, and its gene encoding in children with chronic kidney disease. BMC Res Notes. 2012;5:174. doi: 10.1186/1756-0500-5-174, PMID 22471989
37. Nakagawa N, Yao N, Hirayama T, Ishida M, Ishida H, Wada A, *et al*. Potential impact of renin-angiotensin system inhibitors and calcium channel blockers on plasma high-molecular-weight adiponectin levels in hemodialysis patients. Hypertens Res. 2011;34(5):592-8. doi: 10.1038/hr.2010.282, PMID 21289628
38. Toyama K, Sugiyama S, Oka H, Iwasaki Y, Sumida H, Tanaka T, *et al*. Statins combined with exercise are associated with the increased renal function mediated by high-molecular-weight adiponectin in coronary artery disease patients. J Cardiol. 2014;64(2):91-7. doi: 10.1016/j.jjcc.2013.11.018, PMID 24457019
39. Du J, Xu J, Wang X, Liu Y, Zhao X, Zhang H. Reduced serum CTRP12 levels in type 2 diabetes are associated with renal dysfunction. Int Urol Nephrol. 2020 Dec;52(12):2321-7. doi: 10.1007/s11255-020-02591-y [ePub]. PMID 32734505
40. Gokul M, Umarani G, Esakki A. Green synthesis and characterization of isolated flavonoid mediated copper nanoparticles by using *Thespesia populnea* Leaf extract and its evaluation of anti-oxidant and anti-cancer

activity. Int J Chem Res. Jan 2022;6(1):15-32. doi: 10.22159/ijcr.2022v6i1.197

41. Sarkar S, Sadhu S, Roy R, Tarafdar S, Mukherjee N, Sil M, *et al*. Contemporary drifts in diabetes management. Int J Appl Pharm. 2023;15(2):1-9. doi: 10.22159/ijap.2023v15i2.46792
42. Kamalesh DR, Geetha KM. A review on role of markers in diabetes mellitus and associated micro and macrovascular complications. Int J Curr Pharm Res. Jan 2022;14(1):20-6. doi: 10.22159/ijcpr.2022v14i1.44108
43. Dharani B, Sebastian S, Nazrin S, A. Preventing diabetic kidney disease: A systematic review of current pharmacological approaches. Int J Appl Pharm. 2025;17(1):68-81. doi: 10.22159/ijap.2025v17i1.52956
44. Singh RD, Rahul C, Hitendrapal S. Clinical assessment of antibiotics used in chronic kidney disease: A longitudinal observational study. Int J Pharm Pharm Sci. Oct 2024;16(10):26-9. doi: 10.22159/ijpps.2024v16i10.52103
45. Fadaei R, Moradi N, Kazemi T, Chamani E, Azdaki N, Moezibady SA, *et al*. Decreased serum levels of CTRP12/adipolin in patients with coronary artery disease in relation to inflammatory cytokines and insulin resistance. Cytokine. 2019;113:326-31. doi: 10.1016/j.cyto.2018.09.019, PMID 30337217