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Assessing the levels of Cystatin-C in the serum, along with several biochemical parameters in individuals diagnosed with chronic kidney disease

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ABSTRACT
Background: Chronic Nephron loss and adaptive hyperfiltration in the surviving nephrons are symptoms of chronic kidney disease(CKD), a parenchymal illness caused by a range of acute and chronic stresses. Proteinuria and a gradual decline in renal function are long-term consequences of adaptive hyperfiltration, which damages the glomeruli. Renal function declines without symptoms at first, and kidney failure symptoms do not appear until much later in the disease's progression. Cystatin- C(Cys-C): is a protein produced by the nucleated cells in the body. When kidneys work well, they keep the level of cystatin-C in our blood just right, and high level of this biomarker in blood mean that the kidneys are not working well. Cystatin-C has some advantages over serum creatinine in eGFR. The use of cystatin-C as a confirmatory biomarker in deciding medication dosages or as a confirmatory test in patients with an uncertain diagnosis of chronic kidney disease may be beneficial.Aim: Determine the level Cystatin- C(Cys-C) and other biochemical parameters in sera of patient with CKD and to compare the results with an apparently healthy person of a comparable age group.Patients and methods: This study was a prospective cross-sectional study. There were 85 male in the trial, 55 of whom had CKD, and 30 apparently healthy man included in this study as a control group in Tikrit City over one year time; from June 2024 until the end of November 2024. The blood samples were collected from each man included in this study for the estimation Cystatin- C(Cys-C), were measured using the ELISA kit technique and blood Urea , Creatinine, Uric acid and albumin by using Cobas –Germany. Results: The mean serum level of Cystatin- C(Cys-C), was elevated in CKD patients comparing with control group (13.34 ±1.45, 4.06 ± 1.18 pg/mL). The result was highly significant ($p<0.05$). while the mean serum level of blood urea and serum creatinine was found among CKD patients (155.9 ± 21.3,7.750 ± 2.10 mg/dl), (32.2 ± 6.61, 0.788 ± 0.118 mg/dl) respectively compared with control The result was highly significant ($p<0.05$). Serum uric acid levels showed significant ($p<0.05$) increase even with in normal range in case group at mean ±SD (5.69 ± 1.141mg/dl) compared with mean ±SD of control group (4.497 ± 0.548mg/dl). Serum albumin in case group (mean ±SD) (3.881 ± 0.371g/dl) compared with control group (mean ±SD) (4.477 ± 0.400 g/dl), there was a significant difference at a $p<0.05$. This study also found that there was a positive correlation between S Cystatin- C(Cys-C), with the level of B. Urea serum creatinine in CKD patients.

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1-INTRODUCTION

Deterioration of the renal parenchyma and functional nephron loss are hallmarks of chronic kidney disease (CKD).(1) The process of compensatory development of the remaining nephrons

is triggered by molecular and cellular mechanisms when functioning nephrons are lost.[2] Pathological changes in these processes may cause kidney lesions, which in turn can cause end-stage renal disease (ESRD).[3]

Cystatin-C Cystatin- C(Cys-C): is a protein produced by the nucleated cells in the body. When kidneys work well, they keep the level of cystatin-C in our blood just right, and high level of this biomarker in blood mean that the kidneys are not working well . Cystatin-C has some advantages over serum creatinine in eGFR. The use of cystatin-C as a confirmatory biomarker in deciding medication dosages or as a confirmatory test in patients with an uncertain diagnosis of chronic kidney disease may be beneficial.[4]

Cystatin-C in chronic renal failure:

The glomerular membrane allows almost unfettered passage of cystatin-C, a low-molecular-weight protein with a highly cationic nature (molecular mass: 13 kDa protein).[5] Proximal renal tubular cells reabsorb and catabolize almost all of the filtrated cystatin-C; hence, barely 0.5% of it reaches the urine. [5,6] Muscle mass has a significant impact on creatinine's serum concentration [7], cystatin-C is constantly generated by all nucleated cells [8], and its serum concentration is mostly unaffected by age, sex, and body composition.[9,10] Because of these qualities, cystatin-C has been the subject of much research as a possible substitute for creatinine as an internal serum measure of glomerular filtration rate (GFR). While opinions vary on whether serum cystatin C is more useful than serum creatinine, a number of meta-analyses using cross-sectional data [11,12], and more recent longitudinal data, [13] suggest that it is an excellent marker for detecting rapid changes in GFR and mild renal function impairment (60 to 90 ml/min per 1.73 m^2).[14]

As renal tubular secretion increases, creatinine is no longer able to diagnose stage 2 chronic kidney disease.[15] For estimating GFR in patients with abnormal creatinine production [9], such as those with liver cirrhosis, spina bifida, or advanced age, cystatin-C has been shown to be more accurate than creatinine.[16,17]

Blood Urea: Urea has a molecular weight of 60 g/mol and is a little molecule that dissolves in water. Protein and nitrogen metabolism culminate in it, which includes two nitrogen atoms.[18]

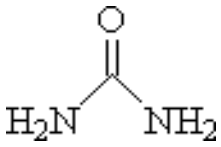

Fig (1): The chemical structure of urea [19]

In uraemic people, urea is the most abundant component in their blood. An inferior indicator of kidney health due to:

a) The rate of synthesis fluctuates; it rises in response to hormones, tissue breakdown, and high-protein meals, and falls in response to liver illness and low-protein diets.

b) 40–50% of filtered urea is reabsorbed in the proximal tubule.[20] An adult typically excretes about 25 grams of urea per day.

Any condition which impairs the elimination of urea by the kidneys can lead to uremia, a buildup of urea and other nitrogen wastes in the blood that can be fatal. To reverse the condition, either the cause of the kidney failure must be removed, or the patient must

undergo blood- dialysis to remove the wastes from the blood. [21]

The B. urea level does not accurately represent the GFR. Because the amount of urea reabsorption by the renal tubules varies with hydration status, blood urea nitrogen is not a reliable indicator of glomerular filtration rate (GFR). Protein consumption and catabolism are two more factors that significantly impact B. urea concentration. Resorption of urea in the proximal tubule causes urea clearance to be lower than GFR.[22] To avoid under- or overestimating GFR caused by tubular reabsorption and over-estimation by creatinine secretion, some suggest combining the two clearances.[23]

Serum Creatinine: A waste product of creatine phosphate breakdown in muscle, creatinine (113 Da) is often generated at a fairly steady rate by the body (depending on muscle mass) and is typically measured in milligrams per kilogram of body weight per day for males and in milligrams per kilogram for females.[24] Creatinine (a blood measurement) is an important indicator of renal health because it is an easily measured byproduct of muscle metabolism that is excreted unchanged by the kidneys. Creatinine itself is produced via a biological system involving creatine, phosphocreatine (also known as creatine phosphate), and adenosine triphosphate (ATP, the body's immediate energy supply).[25] Creatinine is removed from the blood chiefly by the kidneys, primarily by glomerular filtration, but also by proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. If the filtration in the kidney is deficient, blood creatinine concentrations rise.[26] Serum creatinine levels less than 1.5 mg/dL (<133 μmol/L).[27]

Uric Acid: $C_5H_4N_4O_3$ is the chemical formula for uric acid, a substance consisting of carbon, nitrogen, oxygen, and hydrogen. Urates, acid urates, and salts such ammonium acid urate are formed when uric acid reacts with other substances. Urinary uric acid is a natural byproduct of the body's metabolism of purine nucleotides. Among the many health problems linked to elevated uric acid levels in the blood include gout, diabetes, and the development of ammonium acid urate kidney stones.[28]

Albumin: Serum protein levels, particularly albumin, can be significantly altered, often reflecting the severity of the disease and its impact on overall health. Hypoalbuminaemia (low albumin in blood) is common and associated with increased risk of kidney failure, cardiovascular disease, and mortality. [29]

Elevated quantities of albumin in the urine, a condition known as microalbuminuria (MAU), is an early indicator of several kidney diseases, including diabetic renal disease and various glomerulopathies. It is also highly linked to negative effects on cardiovascular health. [30]

PATIENTS MATERIALS AND METHODS

A cross-sectional study situated in a hospital was the design of this investigation. Both the Salah Al-din Health Directorate and the scientific committee of Tikrit University's College of Medicine gave their stamp of approval to the study's methodology and patient sample collection. Research was place from June 2024 until the end of November 2024 at two hospitals in Iraq's Salah Al-din Governorate: Tikrit General Hospital and Balad General Hospital. All patients, whether they were part of the case or control group, gave their explicit agreement to participate in this research.

Study population

Fifty five male Patient with chronic kidney disease and their ages were between (24 -70) years were screened to participate in this study. This study was hospital-based study. The patient with chronic kidney disease that included in this study were from the center and the periphery of Salah Al-din Governorate.

The control group for this research consisted of thirty adults from both the central and peripheral areas of Salah Al-din Governorate who were otherwise healthy, had no history of medical problems, and had no relatives with chronic kidney disease. The participants' ages were similar to those of the CKD patient.

Samples Collection

After morning, patients and controls were each given a six-milliliter venous blood sample via sterile disposable syringe. The samples were then left to clot at room temperature before being centrifuged at 3000 rpm. The serum supernatant was then removed, divided into aliquots in plastic gel tubes, and stored in a deep freezer at -20 0C until the time of estimation Cystatin- C(Cys-C), were measured using the ELISA kit technique and blood Urea , Creatinine, Uric acid and albumin.

Statistical analysis:

All the date collected in this study were analyzed by using the student t-test, the mean, standard deviation, and P-value was also considered. The significance was considered at a P value of less than 0.05.

RESULTS AND DISCUSSION

The serum Level of Cystatin-C in patient with chronic kidney disease and control group.

In this study, the mean serum level of Cystatin-C was found among patients with chronic kidney disease was (13.34 ±1.45ng/mL) compared to control group which was (4.06 ± 1.18ng/mL). The result was highly significant at a P value of 0.05, as shown in the following table.

Table (1): The mean and standard deviation of serum Cystatin-C in patient with chronic kidney disease and the control group.

Study groups	No.	level of Cystatin-C (ng/mL) Mean ± SD	P. value
Cystatin-C patients	**55**	**13.34 ±1.45**	
Control group	**30**	**4.06 ± 1.18**	**p<0.05**

Table(1) shows the mean differences of Cystatin-C levels (ng/mL) in patient with CKD and control group. There was a significant differences between means of Cystatin-C level of study group at a p value less than 0.05, the mean ± SD for patients (13.34 ±1.45ng/mL), the mean serum levels of Cystatin-C in CKD patient, was significantly higher than that of the control person (4.06 ± 1.18ng/ mL).

These findings could be attribute to low-molecular weight of this protein, and decrease renal clearance resulting from

decline in GFR. Cystatin-C production appears to be more uniform in different populations than creatinine production, which has been shown to exhibit considerable heterogeneity due to variables unrelated to glomerular filtration . Cystatin-C is less influenced by age, gender, ethnicity, muscle mass, protein intake, renal tubule management, and extrarenal elimination compared to creatinine. [31] This study was in agreement with old study, that noticed that the serum cystatin C is an earlier and more accurate biomarker of GFR than creatinine in many patient populations.[32] Also previous study show that Cystatin-C is useful to detect individuals with CKD who show a little reduction in GFR as compared to serum creatinine.[33] Urinary Cys-C levels correlated with urinary albumin excretion rate (UACR), and GFR. It is linked to subclinical tubular injury and can be an earlier marker of kidney involvement, even before albuminuria and it is less influenced by non-renal factors.[34] Therefore, Urinary Cys-C is useful biomarker for early diagnosis of diabetic nephropathy.[35] Cystatin C is produced by all human nucleated cells, and although it is affected by some non-GFR determinants e.g: in inflammation, thyroid dysfunction, smoking, and obesity.[36]

The mean serum level of B. urea that result in this study was found among patient with chronic kidney disease (155.9±21.3 mg/dl) and the mean in control group was (32.6 ± 6.61 mg/dl). The result was highly significant ($p<0.05$), Table (2).

Table (2): The mean and standard deviation of serum level of blood urea and creatinine in the serum of patient with chronic kidney disease and the control group

Study group	No.	B. urea (mg/dL) Mean ± SD	level of Creatinine (mg/dL) Mean ± SD
Chronic kidney disease patients	**55**	155.9 ± 21.3	7.750 ± 2.10
Control group	**30**	32.2 ± 6.61	0.788 ± 0.118
P value		p<0.05	p<0.05

Table (2) showed that the highest mean of blood urea was recorded in renal failure patients; with (mean ±SD) (155.9 ± 21.3mg/dl) as compared with control group (mean ±SD) (32.2 ± 6.61mg/dl) the result was significant different at a $p<0.05$). Recent study reported that the level of urea in serum is used as an indicator for CKD severity and dialysis adequacy in clinical settings.[37]

The mean serum level of creatinine that present in this study found among patient with chronic kidney disease was (7.750 ± 2.10 mg/dl) and the mean was in healthy control group (0.788 ± 0.118 mg/dl). The result was significant ($p<0.05$), Table (2).

As show in table above, Serum creatinine levels showed significant ($p<0.05$) increase in case group at mean ±SD (7.750 ± 2.10 mg/dl) compared with mean ±SD of control group (0.788 ± 0.118mg/dl). In recent research serum creatinine establish used in the diagnosis of renal failure, because the amount of muscle mass proportional to the amount of creatinine produced and excreted as reported Prodyanatasari A, Purnadianti M.[38]. This study demonstrated that the mean level of S. uric acid that recorded

among patient with chronic kidney disease was (5.69 ± 1.141 mg/dl) and the mean was in healthy control group (4.497 ± 0.548 mg/dl). The result was highly significant(p<0.05),as show in table (3).

Table (3): Level of serum uric acid in patient with chronic kidney disease and the control group

Study groups	No.	level of Cystatin-C (ng/mL) Mean ± SD	P. value
Chronic kidney disease patients	**55**	**5.69 ± 1.141**	
Control group	**30**	**4.497 ± 0.548**	**p<0.05**

Serum uric acid levels showed significant (p<0.05) increase in case group even with in the normal concentration range at mean ±SD (5.69 ± 1.141mg/dl) compared with mean ±SD of control group (4.497 ± 0.548mg/dl) as show in table (3). This findings was in agreement with other research; who said that the increase in serum uric acid (SUA) levels are commonly seen in patients with metabolic syndrome and are widely accepted as risk factors for hypertension, gout, non-alcoholic fatty liver disease, chronic kidney disease (CKD), and cardiovascular diseases.[39] This study are in line with the results of research, Which concluded that vitamin D deficiency was related to hyperuricemia and suggested a bidirectional association between UA and vitamin D. primary hyperparathyroidism had increased SUA levels . It was also shown that vitamin D supplementation can reduce SUA levels in patients with prediabetes and hyperuricemia.[40]

The serum Level of Albumin in patient with chronic kidney disease and control group.

The mean serum level of albumin that present in this study found among patient with chronic kidney disease was (3.881 ± 0.371 g/L) and the mean was in healthy control group (4.477 ± 0.400 g/L). The result was significant (p<0.05), Table (4). As show in table (4),it showed that there was mean of serum albumin in case group (mean ±SD) (3.881 ± 0.371g/dl) compared with control group (mean ±SD) (4.477 ± 0.400 g/dl) there was a significant difference at a p<0.05 . This study are in line with the results of research that reported that the reason of this result is due to treatment by maintenance haemodialysis or renal transplantation usually corrected the hypoalbuminaemia.[41]

Table (4): The mean and standard deviation of serum level of albumin in patient with chronic kidney disease and control group

Study groups	No.	level of Cystatin-C (ng/mL) Mean ± SD	P. value
Chronic kidney disease patients	55	3.881 ± 0.371	**p<0.05**

Control group	30	4.477 ± 0.400

Correlation Between serum Cys-C Level and B. Urea Level in patient with CKD: This study presented that there was a positive correlation between S. Cys-C level and level of B. Urea in CKD patients , Fig (2).

Correlation Between serum Cys-C Level and S. creatinine Level in patient with CKD : In individuals with chronic kidney disease (CKD), this research discovered a favourable connection between serum cystatin C and serum creatinine levels Fig(3).

Correlation Between serum Cys-C Level and S. Uric acid Level in patient with CKD: This presented study, it reported that there was a positive correlation between S. Cys-C level and S. UA and in CKD patients , Fig (4).

Correlation Between serum Cys-C Level and S. Albumin Level in patient with CKD: This presented study, it reported that there was a positive correlation between S. Cys-C level and S. UA and in CKD patients , Fig (5).

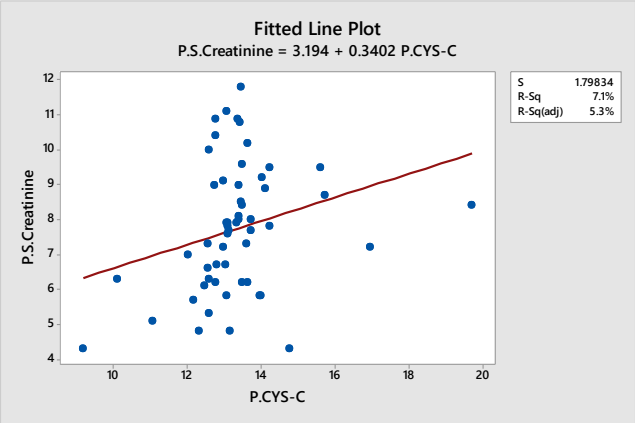

Fig (2): Correlation between level of S. Cys-C and B. Urea in Patient with CKD.

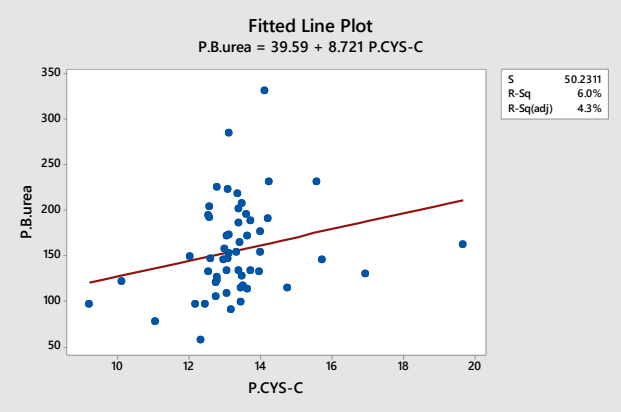

Fig (3): Correlation between level of S. Cys-C and S. Creatinine in Patient with CKD.

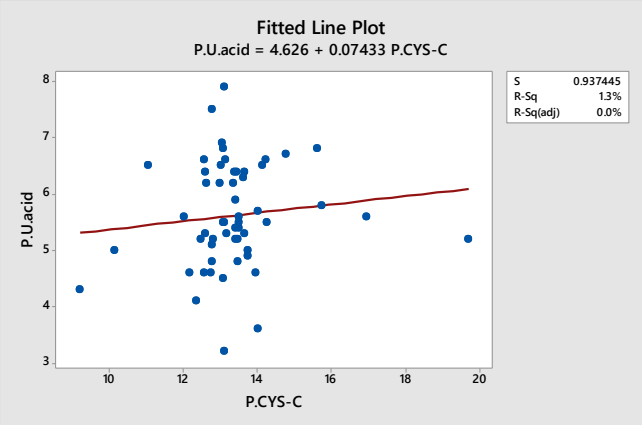

Fig (4): Correlation between level of S. Cys-C and S. Uric acid in Patient with CKD.

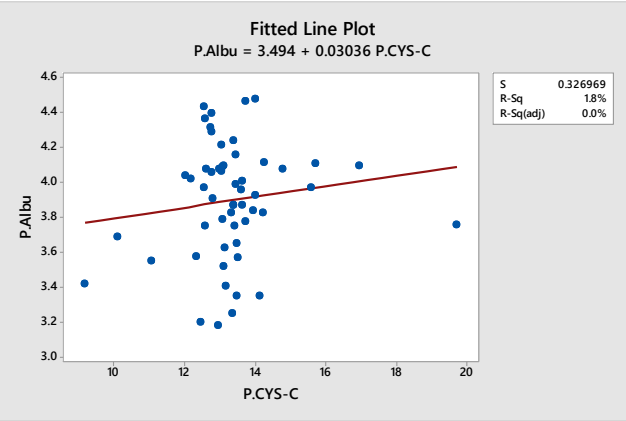

Fig (5): Correlation between level of S. Cys-C and S. Albumine in Patient with CKD.

CONCLUSION

Cystatin -C is considered a good marker for evaluation of CKD ,with appositive correlation of, B. Urea, S. Creatinine ,and S. Uric acid, and albumin.

RECOMMENDATIONS

Uses of Cys-C test with creatinine routine screening especially in elderly, individual with low or abnormal muscle mass. Making further studies used a new biomarker to improve early diagnosis and reduce progression of CKD, and arrange programs for the early detection of CKD to reduce the cost of socioeconomic problems.

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