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Determination of Cystatin C Level in a Sample of Patients with Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) effects around one-third of the population and is frequently under recognized by patients and clinicians. GFR of less than 60 mL/min/1.73 m2, A minimum of 30 mg of albuminuria per 24 hours, Hematuria or structural abnormalities are signs of kidney damage such like polycystic kidney disease or dysplastic kidneys that persists for more than 3 months. The purpose of this research was to examine the efficacy of cystatin C as a measure of renal function in individuals. Cystatin C, Creatinine, urea, and uric acid levels were measured in 225 blood samples (150 patients and 75 controls). Cystatin C was measured as enzymatic link absorbance assay and the measurements of urea, creatinine, and uric acid were performed using the Cobas c311. Cystatin C levels, urea, serum creatinine, and uric acid were found to show high significant differences ($p < 0.01$) between the patient and control. Cystatin C is useful to detect individuals with CKD who show a little reduction in GFR as compared to serum creatinine. Serum Cystatin C, urea, uric acid, and Creatinine levels all rise as eGFR falls. Serum Cystatin C could be utilized to evaluate people who have poorly managed diabetes mellitus or high blood pressure when the serum creatinine level is inconclusive.

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1. Introduction

CKD is characterized by a decreased glomerular filtration rate, increase urine albumin secretion, or even both, and is a major public health concern, Globally, it is predicted to be between 8% and 16% [1]. Long-term all cardiovascular mortality, development of kidney disease, acute renal injury, cognitive deterioration, anemia, mineral and bone problems, and fractures are all complications, Diabetes remains the main form of persistent renal disease worldwide, but natural and environmental pollutants, as well as its diverse causes, are more widespread in a few places [2]. The poorest people are the most vulnerable. The measurement of glomerular filtration rate and albuminuria is used to identify end stage chronic kidney disease, Globally, CKD is maximum typically attributed to diabetes and/or hypertension, However, different reasons such as glomerulonephritis, infections, and environmental triggers exist (consisting of air pollution, natural remedies, and pesticides) are not unusual place in Asia, sub-Saharan Africa, and plenty of growing countries [3, 4]. Calculating the true glomerular filtration rate by using external filtration markers is time-consuming and inefficient, Therefore, depending on plasma creatinine concentrations, values are estimated [5]. Cystatin C (CysC), an endogenous cysteine proteinase inhibitor with a molecular weight of 13 kDa, is a member of the protein family that has crucial function in the intracellular catabolism of diverse peptides and proteins [6]. Cystatin C has long been used to assess renal function. although its clinical application in comparison to serum creatinine remains quite limited, the generation of Cystatin C inside the body is indeed a stable process that is untouched by renal problems, increased protein catabolism, or dietary factors, Moreover, unlike creatinine, it does not change with age or muscle, these biochemical features allow for unrestricted filtration in the kidney's glomerulus, followed by reabsorption and metabolism in the proximal tubule, As a result of these, Cystatin C has now been proposed as an acceptable endogenous measure of glomerular filtration rate, over the last decade Cystatin C has indeed been widely employed as a research tool to understand how function influences health outcomes, especially in the supposed healthy range of kidney function (glomerular filtration rate [GFR] of 60 ml/min/1.73 m2) [7]. Among the many biochemical markers identified, Cystatin C has indeed been recommended as a potential marker that could aid in the detection of initial nephropathy, Cystatin C is a Cysteine protease blocker with a small molecular weight that is generated by practically every nucleated cell in the body, it is easily filtered within the glomerulus and reabsorbed in the renal tubule and decomposed [8]. Cystatin C outperforms S.Cr in estimating kidney function since it is unaffected by aging, gender, or body weight. [9]. S. Cr is synthesized in the muscles, as well as the amount produced is determined by muscle mass, it does not attach to plasma proteins and is readily filtered by the kidney, but it is also released by the kidney tubules, one major disadvantage of S. Cr as a GFR marker is that it is not a sensitive indicator to detect mild GFR, requiring timed urine specimen collection and the use of a formula that needs serum and urine Creatinine measurements [10]. Because of the ease of estimation, S.Cr is routinely used by clinicians to evaluate renal disease development and therapy response, there are several equations for calculating eGFR

Nomenclature & Symbols			
CKD	Chronic kidney disease	SCr	Serum Creatinine
SCysC	Serum Cystatin C	SPSS	Statistical Package for Social Science
GFR	glomerular filtration rate	MCP	Monte Carlo - test
BUN	Blood urea nitrogen	U.A	Uric acid
ESRD	End Stage Renal disease		

from a singular S.Cr measurement. Furthermore, S.Cr is just not very accurate in detecting initial stages of renal illness; a decline in Glomerular Filtration Rate (GFR) of more than 50% is required before SCr levels climb over the typical upper reference range [11]. In skeletal muscle, creatinine is mostly made up of creatine and phosphocreatine. Creatinine is excreted freely by the kidneys and is useful in interpreting kidney function, the most prevalent methods to measure serum creatinine are based on the Jaffe reaction, in which creatinine interacts with picrate in an alkaline medium and the generated orange complex is measured spectrophotometrically [12]. Some variables, such as high amounts of serum protein, glucose, and keto acids, interact with creatinine doses (diabetic ketoacidosis), the lack of specificity is a key issue with this approach, which has been mitigated by the use of kinetic assays, automatic analyzers evaluate color creation in between 20 and 80 seconds, while enzymatic approaches are thought to be more specific [13]. Rhabdomyolysis and consuming raw meat can significantly raise serum creatinine levels, which can impact urine creatinine levels [14,15]. Due to these creatinine-related drawbacks, Other endogenous GFR indicators have been investigated, Cystatin C has so far proven to be the most promising marker with the potential to replace creatinine [16, 17]. Blood urea does have a molecular weight of 60 g/mol, is a tiny, water-soluble molecule with 2 nitrogen atoms, and is it product by proteins and nitrogen metabolism, urea is the most abundant substance in the blood of uremic people [18]. A serum urea level can be represented as a molar concentration or even as a mass concentration the levels of serum mass concentration can be defined for the entire urea molecule or for nitrogen equivalents [blood urea nitrogen (BUN)] in a 60/28 ratio [19]. BUN levels are much higher in patients with chronic kidney disease and also in patients with terminal renal failure they reach concentrations before dialysis that can be ten times or more the upper normal value [20]. Uric acid is indeed the last oxidation outcome of purine metabolism and is eliminated through the kidneys, as a result, patients with reduced glomerular filtration rates have higher serum U.A levels, U.A the final result of purine metabolism, has therapeutic significance because it is exceedingly insoluble, especially in the acidic condition of the distal nephron, which causes situations of accelerated purine catabolism to increase the urate burden in the kidney, this leads to an intrarenal precipitate [21]. Any functional decline that affects glomerular filtration rates and tubular reabsorption indirectly causes uric acid elevation, but a reduction in GFR can also cause level UA elevation [22]. However, it has recently been postulated that uric acid may have a role in the etiology of chronic kidney disease as well as acute renal violence [23]. The study's goal was to see how effective cystatin C was as a measure of CKD patients.

2. Materials and methods

2.1. Collection of samples

Five milliliters of blood were drawn from each subject via vein puncture with disposable syringes. The blood was separated by centrifugation at 3000 rpm for 10 minutes after the blood sample was deposited in a gel disposable tube to determine (Cystatin C, Urea, creatinine, and uric acid). Cystatin C level was detected by using the Elisa kit (My BioSource-USA) and assessment of other tests such as blood urea, S. Creatinine and S. uric acid by using a chemical analyzer instrument (Cobas C311).

2.2. Study design

This study was done on 150 patients with chronic kidney disease and 75 apparently healthy persons (control). All of these samples were distributed in Baghdad, from the medical city-Baghdad hospital, between November 2021 and March 2022, in order to study some biochemical markers in patients with chronic renal disease and healthy controls. The study used 150 samples to measure Cystatin C levels and compare them to healthy people, as well as measure urea, S.Cr, and U.A levels and compare them to healthy people. The Medical City of Baghdad Teaching Hospital's laboratories were used for this study.

2.3. Statistical analysis

The "Statistical Package for Social Science (SPSS) version 26.0 was used to revise, code, and analyse the data. - Using for data presentation: Method of presenting mathematics (Mean and Standard Deviation). Tabular presentation of data (Simple &Complex frequency distribution Table).
And for analysis of data using t- test and Monte Carlo - test (MCP).
In each test, the comparison of significant (p-value) was assessed as follows:

P-Value of garter than 0.05 ($P>0.05$) was non-statistically significant (NS).
P-Value of less than 0.05 ($P<0.05$) was statistically significant (S).
P-Value of less than 0.01 ($P<0.01$) was highly statistically significant (HS).

3. Result

3.1. Age and Gender distribution of the study groups

The results in the Table 1 showed that the distribution of study group according to age and gender. The age ranges (10-29 years) are represented by 12 (8.0 percent) and (30-39 years) by 41 (27.3 percent) in this table. Age range (40-49 years) 55 (36.7 percent) While the age range (50-60) was 42 (28%) Among the 150 cases of chronic kidney disease, there were 60 (40.0 percent) males and 90 (60.0 percent) females.

Table 1 Distribution of Study groups according to Age groups(years) by Gender

Age groups(years)		Control group Gender			Patients group Gender		
		Male	Female	Total	Male	Female	Total
(10-29)	No.	9	10	19	7	5	12
	%	12.0%	13.3%	25.3%	4.7%	3.3%	8.0%
(30-39)	No.	11	16	27	14	27	41
	%	14.7%	21.3%	36.0%	9.3%	18.0%	27.3%
(40-49)	No.	8	10	18	14	41	55
	%	10.7%	13.3%	24.0%	9.3%	27.3%	36.7%
(50-≥ 60)	No.	6	5	11	25	17	42
	%	8.0%	6.7%	14.7%	16.7%	11.3%	28.0%
Total	No.	34	41	75	60	90	150
	%	45.3%	54.7%	100.0%	40.0%	60.0%	100.0%

3.2. Distribution of Serum Cystatin c(ng/ml), Urea, S. Creatinine& Uric acid (mg/dl) in the Patients and Control Group

The results in the Table 2 showed there were highly significant p< 0.01 differences in serum Cystatin C and urea, creatinine and uric acid levels in comparison to the patient and control groups (410.15±127.02 Vs. 156.72 ± 46.39 mg/dl) and (155.03± 67.67 Vs. 30.26 ± 6.61), respectively. There were highly significant differences in mean serum creatinine (5.89 ± 3.83 Vs. 0.72 ± 0.13) and mean serum uric acid (6.88 ± 1.84 Vs. 4.38 ± 0.69) between the patient and control groups.

Table 2 Comparison between the (Mean ± Std.) value of Cystatin C, Urea, S. Creatinine and S. Uric acid for study groups

	Control	Patients	
	Mean ± Std.	Mean ± Std.	P-Value
Cystatin C (ng/ml)	156.72±46.39	410.15±127.02	.000 (HS)
Urea (mg/dl)	30.26±6.61	155.03±67.67	.000 (HS)
S. Creatinine (mg/dl)	0.72±0.13	5.89±3.83	.000 (HS)
S. Uric acid (mg/dl)	4.38±0.69	6.88±1.84	.000 (HS)

4. Discussion

It is critical to detect CKD in its early stages. SCr and GFR are the two markers that are now used to evaluate, predict, and track treatment response. SCr is a superior metric to rely on due to its low cost, ease of estimation, and specificity. Furthermore, Creatinine" has considerable disadvantages. SCys C, an alternative marker with few limitations, was examined and compared to SCr. One of the most infective CKD can occur in any age group, and these results agree with [24] who found that mean ages group of (40- 49) years was largest these results agreed with [25] Moreover, other studies that agreed with this study were done by [26], who reported a mean age of (50 -≥ 60) years The gender disparity in CKD patients may be explained by the fact that females in these studies may have had greater than males [27].

The higher rate of CKD infection among females may be due to CKD risk factors such as hypertension, diabetes, proteinuria, renal anatomy, and change hormones, which have been observed to have differing impacts on men and women [28]. There were highly significant differences p< 0.01 between the patient and control groups in the levels of serum Cystatin C, Urea, Creatinine, uric acid. These results are compatible with another study done by [29] who reported that there were significant differences in the mean Cystatin C level and creatinine between the chronic kidney patients and control groups. Other studies that agreed with this study were done by [30] who reported evaluating Cystatin C levels in chronic kidney disease.

In the present study, there was a highly significant difference in the mean of serum urea in patient and control groups. These results agreed with other studies done by [31], [10]. Furthermore, the present study comes in compatible with another study in There was a statistically significant difference in serum uric acid mean between the patient and control groups. This study agrees with other studies done by [32]. Serum uric acid concentrations rise in chronic kidney disease (CKD) due to decreased glomerular filtration rate (GFR). Uric acid is just a marker of reduced estimated GFR (eGFR) or is coincidentally related with worse outcomes in CKD [33].

A decrease in renal function results in a fall in GFR and an increase in cystatin C and other renal function markers, creatinine and blood urea are two examples. These levels rise because the kidneys are unable to filter the blood correctly at a regular rate, allowing it to accumulate in the blood. [34]. Improvements in renal function, on the other hand, are likely to result in an increase in GFR, this may result in a reduction in cystatin C, creatinine, and urea levels due to the kidneys' ability to effectively eliminate them from the blood. Creatinine synthesis varies greatly depending on muscle mass and dietary variables. The glomeruli filter it, but the renal tubules also secrete it. This tubular secretion accounts for about 20% of all creatinine output by the kidney and can rise when GFR falls. Each of these factors explains why a creatinine level may not have been an accurate measure of GFR, particularly at lower levels. [35].

It discovered that having an eGFR of 60 ml/min per 1.73 m2 was only related to an elevated risk of death, cardiac diseases, and heart problems if verified by cystatin C. Individuals with reduced GFR due to creatinine alone face the same risks as those with normal GFR. Thus, based on this different risk for cardiovascular and death outcomes, cystatin C may play a major diagnostic role in distinguishing both "higher risk" and "lower risk" patients for CKD sequelae with a creatinine-based eGFR of 60 ml/min per 1.73 m2. National and international organizations have advocated for improved CKD identification by estimating GFR using creatinine-based equations. Screening tests that balance sensitivity and specificity are required for early detection. Although creatinine-based eGFR equations may be sensitive for identifying those at risk for poor kidney disease outcomes, cystatin C significantly increased specificity in these multi-ethnic and older adult populations. This shows that cystatin C could be used as a confirmatory test for CKD diagnosis.

The concentration levels of cystatin C in the bloodstream are stable while the kidneys are functioning normally [36]. Therefore, as renal function deteriorates, concentrations start to increase. The elevation in cystatin C happens during the fall of GFR and is frequently observed before a significant reduction in renal function (GFR). Although cystatin C rates vary with GFR, there has been some interest in screening for cystatin C as a technique of assessing kidney function. Creatinine, a consequence of muscle metabolism detected in blood and urine, urea nitrogen (BUN), and eGFR are three tests that are now in use (a GFR estimate is usually calculated from a blood creatinine level). Despite creatinine, Cys C is not greatly impacted by muscle mass (and thus gender or age), race, or diet, leading to the hypothesis that it could be a more trustworthy marker of kidney function and could be used to establish a more accurate GFR estimate [37]. In persons with established or suspected renal disease, the cystatin C test could be used instead of creatinine clearance to evaluate for and monitor kidney impairment.

For the past fifteen years, it's been well documented that cystatin C is a significant prognostic marker of morbidity and death in a wide range of patients. It's been linked to the advancement of final renal disease and death in diabetics suffering from acute kidney injury, CKD [38, 39], and dialysis patients.

5. Conclusion

In this research, we investigated and compared cystatin C, urea, and serum creatinine as indicators of GFR in extremely sick patients who were unstable. According to this study, serum Cys C is an accurate real indicator of GFR in these people. Whether this result is confirmed or not, the ease with which plasma CysC may be identified and the low cost of this test imply that it could eventually replace the S.Cr test as the diagnostic biomarker of preference for measuring GFR in clinical practice. S. Cys C is a sensitive indication of minor fluctuations in GFR and may be preferable to creatinine in clinical practice for evaluating this parameter in critically ill patients**.** However, the number of laboratory and clinical imprecisions in Scr the most commonly used reference for determining GFR, is longer. Cystatin C has been shown being more dependable than creatinine levels in a variety of patient demographics. It detects prior, large subtle abnormalities in kidney function, the price and therapeutic importance of which are still being determined Cystatin C is very well proven as a distinct indicator of morbidity, death, and progression to end stage renal disease (ESRD). in a number of participants, opening up several new avenues of investigation beyond correct GFR estimation.

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Ethical clearance: Informed consent was obtained from patients when samples were collected.

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