The Role of Interelukin -6, Resistin and Cystatin C in Iraqi Patients with Chronic Kidney Disease

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Abstract— **Background: Studies have found that Chronic Kidney Disease (CKD) is fairly prevalent throughout the world. Due to their comorbidities and lifestyle, patients receiving hemodialysis for chronic renal illness are more prone to show changes in some biochemical indicators. The present work was conducted to study the role of some biochemical factors, including interleukin-6, resistin, and cystatin C. and the relationship between cystatin C and creatinine in order to track the progression of individuals with chronic renal disease.**

Objective: Due to the rise in instances of chronic kidney disease in Mosul city, the primary objective of the study was to examine levels of interelukin_6, Resistin , Cystatin C and some biochemical parameters in the blood of patients and compare their levels in healthy people, and to investigate the relationship of serum interelukin _6 with the development of the disease.

Materials and methods: The study enrolled (80) cases of well diagnosed chronic kidney disease Iraqi patients, while the healthy group included (79) individuals. The age of both groups ranged between 18 and 55 years. Blood samples (5ml) have been used for serum separation , which is in turn used in the biochemical analysis, which included determination of biochemical parameters (interleukin-6, resistin, and cystatin C) using the protocol of ELISA kit, while estimated Cystatin C / Creatinine ratio .

Results: The study's findings revealed that the levels of interleukin-6, resistin, cystatin C, and creatinine had increased significantly ($P \leq 0.01$). The cystatin C/creatinine ratio was found to be significantly ($P \leq 0.01$) higher in the patient group as compared to the control group, A substantial significant at ($P \leq 0.01$) decrease in albumin concentration was noted, whereas C-reactive protein concentration and the C-reactive protein/albumin ratio did not differ significantly at ($P \leq 0.05$) between the patient group and the control group. A correlation study has been done between the parameters (interleukin-6, resistin and cystatin C) and other biochemical parameters. IL-6- shows a significant positive correlation with cystatin C and the cystatin C/ Creatinine ratio($r = 0.504$, $p = 0.02$ and $r = 0.5$, $p = 0.01$ respectively), while non significant with other parameters ,there is a highly significant positive association between Resistin and creatinine as well as between Cystatin C /creatinine ratio in the group of patients with CKD ($r= 0.305$, $p=0.01$, and $r= 0.30$, $p=0.05$, respectively). On other hand there was non significant correlation with other parameters. The results revealed the presence of significant positive correlation of Cystatin C associated with IL-6- and Cystatin C / Creatinine ratio ($r= 0.504$, $p=0.02$ and $r= 0.63$,$p=0.00$ respectivly), There was non significant correlation between (IL-6- ,Resistin, Cystatin C) and other paramerters .

Conclusion: A high concentration of IL-6, Resistin, and Cystatin C is associated with chronic kidney disease. The development of the disease is tightly correlated with the studied biochemical characteristics.

Keywords: Chronic kidney diseases, interleukin -6-, hemodialysis, resistin , Cystatin C.

I. INTRODUCTION

Over the past forty years, the prevalence of chronic kidney disease (CKD) has increased to the point where some have called it a pandemic [1]. With a 9.1% prevalence worldwide, CKD is a major public health concern [2]. It is a non-infectious disease characterized by several physiological problems, including deteriorating kidney function and a gradually declining glomerular filtration rate [3]. Changes in the kidneys' structure or function, or both, occur with chronic renal disease, which impacts the patient's health [4]. Everywhere in the globe, the chronic renal disease frequency and associated risk factors are rising, along with the demand for end-stage kidney treatment [5]. There is a significant build-up of fluids, electrolytes, and toxins that are typically eliminated by the kidneys and cause uremic syndrome. If the toxins are not eliminated by renal replacement therapy, which includes dialysis or kidney transplantation, this illness results in mortality [6]. The pro- and anti-inflammatory properties of the cytokines [7], known as IL-6, are produced from T lymphocytes, endothelial cells, fibroblasts, and monocytes [8]. IL-6 consists of 184 amino acids with double bonds Sulfide [9]. Patients with renal disease, particularly CKD, have been shown to have higher levels of the IL-6 cytokine family in their kidney tissues, the same in Obstructive nephropathy, diabetic nephritis, and glomerulonephritis [10]. Acquarone *et al*. noted high levels of Resistine in patients with chronic kidney disease (CKD) and/or related clinical problems [11]. Resistin, a 108-amino acid hormone with a crystalloid structure and a member of the rescission-like molecule (RELM) family of cysteine-rich proteins, is distinguished by a single location that contains 10–11 cysteine groups [12]. It is an adipocyte peptide hormone discovered in 2001. The role of Resistin in IR for PCOS is still controversial [13]. The term "Cystatin" was first used in 1981 by Barrett to describe a natural protein element that demonstrated the ability to inhibit lysosomal cysteine proteases. Since then, many proteins with the same function have been described and classified as Cystatin superfamily [14]. All nucleated cells release serum Cystatin C into the bloodstream, readily filtered by kidney glomeruli, processed by the proximal

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tubule, and recognized as a sign of renal failure [15]. According to Dönmez *et al.,* Cystatin C may be the most accurate and reliable marker of chronic kidney disease because it is unaffected by age, height, and BMI. Studies suggested that using Cystatin C may help GFR play a more significant role in diagnosing patients with Stage I to III chronic renal disease [16]. Our study aimed to investigate the role of IL-6, Resistin, Cystatin C, and Cystatin C/ Creatinine ratio in Iraqi patients with chronic kidney diseases.

II. Materials And Methods

Study Subjects

Eighty anemic patients with chronic renal diseases of both sexes (34 males and 46 females) aged (18-55years) participated in the study. They were undergoing kidney dialysis at the Ibn-Sena Teaching Hospital in the Nineveh Governorate. In addition, the control group of both sexes consisted of 79 healthy individuals ranged in age from 18 to 55 years and the study's rules were in accordance with the ethics committee for the college of science at the University of Mosul and the Nineveh Health Department. To participate in the research, each subject was given a questionnaire asking for their informed consent.

Sample Collection

Samples were taken from the Iraqi visitors to the dialysis unit over the course of eight months, starting in November 2020. Serum samples were taken after extracting 5 ml of venous blood in a clean dry tube, and allowed to clot for 15 minutes at 25 °C. After that, the blood was centrifuged for 10 minutes at 3000 xg to separate the serum from the rest of the blood. Sera aliquots were put in Eppendorf tubes and kept frozen at -20°C prior to laboratory procedures. Patients with cardiovascular issues and those using cytotoxic drugs were excluded from the study.

Estimation Of The Biochemical Markers

Human IL-6 and resistin concentrations were determined using an ELISA kit (enzyme-linked immunosorbent assay) according to manufactures instruction (BT LAB/ China), while Cystatin C was measured by the same technique using the kit supplied by (My BioSource /USA) . Serum Creatinine was determined by Colorimetric Method (With Deproteinization) using a manual kit that was tested in accordance with the prescribed technique (Randox/UK).

Statistical Analysis

The pre-built statistical program SPSS version 19 was utilized to analyze the data. The mean standard deviation of all findings was reported.The results were statistically evaluated using t-test to discover the significant differences between the study groups, and the correlation coefficient was also employed. The probability level $p \leq 0.01$ was regarded significant while $p \leq 0.05$ was declared non-significant. (Pearson's moment correlation) in order to establish whether there is an actual correlation between the variables under study.

III. Results

This study included 159 participants in total . Eighty individuals with in the study group had chronic kidney disease , Table 1 displays the attributes of the research population.

The prevalence of the disease in patients over 40 years of age is (82.5%) higher than in other age groups, A slight prevalence of the disease in females (57.5%) compared to males(42.5%), Non-significant effect of family history 8%, Slight effect of smoking 15% and Non-significant effect of alcoholism among patients 5% Table 1.

The values of interleukin-6, resistin, cystatin C, and creatinine had increased significantly ($P \leq 0.01$). The cystatin C/creatinine ratio was found to be significantly ($P \leq 0.01$) higher in the patient group as compared to the control group, A substantial significant at ($P \leq 0.01$) decrease in albumin concentration was noted, whereas C-reactive protein concentration and the C-reactive protein/albumin ratio did not differ significantly at ($P \leq 0.05$) between the patient group and the control group Table 2. IL-6- shows a significant positive correlation with cystatin C and the cystatin C/ Creatinine ratio($r = 0.504$, $p = 0.02$ and $r = 0.5$, $p = 0.01$ respectively), while non significant with other parameters ,there is a highly significant positive association between Resistin and creatinine as well as between Cystatin C /creatinine ratio in the group of patients with CKD ($r= 0.305$, $p=0.01$, and $r= 0.30$, $p=0.05$, respectively). On other hand there was non significant correlation with other parameters. The results revealed the presence of significant positive correlation of Cystatin C associated with IL-6- and Cystatin C / Creatinine ratio ($r= 0.504$, $p=0.02$ and $r= 0.63$,$p=0.00$ respectivly), There was non significant correlation between (IL-6- ,Resistin, Cystatin C) and other paramerters Table 3. Urea, creatinine, and cystatin C all have AUC, sensitivities, and specificities of 1, as well as the measurement of serum resistin and IL-6, aid in the tracking of the severity of the sickness. The results of this investigation showed that IL-6 and CRP/albumin *10-4, at an AUC of greater than 0.9 Table 4 and Fig 4.

IV. Discussion

Table (1) provides specific clinical characteristics of the individuals. The results agree with those reported by Huda et al. [17]. Hasan et al. findings are compatible with ours as they stated that the prevalence of CKD patients at age 40 was about (16.5%) [18].

CKD patients have a slight prevalence in females over males, which is consistent with the studies by Goldberg et al. [19], given that males have more muscle mass and produce more Creatinine than women do, this can be explained by the fact that men have higher levels of renal function than women depending on a particular level of Creatinine [19]. A no significant effect of the family history was observed, with a small percentage (8%) in patients with chronic kidney disease. Smoking affects the risk of CKD (Table 1) in that the percentage of smokers is 15%, which is consistent with the study of Choi et al. [20]. Who indicated an increased risk of disease for smokers compared to non-smokers. Alcoholism has no significant effect on patients with chronic kidney disease, with a small percentage (5%).

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Table (2) shows that CKD patients had significantly (P≤ 0.01) increased levels of IL-6, Resistin, Cystatin C, Creatinine, and the ratio of Cystatin C to Creatinine as compared to control. Intereukin-6 concentrations were significantly higher in the CKD group than in the control group. Protein insufficiency may be a factor for the elevated levels of IL-6 found in chronic renal disease patients; as muscle clearance declines, IL-6 accumulates more widely throughout the body. In addition to the dialysis catheter, vascular fistula, or perhaps even the dialysis itself, CKD patients are more susceptible to bacterial or viral, where foreign bodies promote inflammation and hence increase the level of the relevant cytokine [21]. Therefore, and according to the above reasons, it may be the main cause of elevation of IL-6 in CKD patients, which is demonstrated in the present findings due to the pro-inflammatory properties [22]. The findings show that the patients' group has a significantly higher resistin concentration than the control group. This finding is corroborated by earlier research that found a correlation between rising Resistin concentration and declining GFR. In other words, a decline in GFR is accompanied by increased Resistin levels in CKD patients. It is important to note that Resistin is a 12.5 kD protein with properties of renal clearance similar to β2- microglobulin (13.7 kDa) [23]. A decreased renal Resistin filtration or renal Resistin catabolism, consistent with a diminishing GFR, may cause elevated Resistin concentrations in CKD patients [24]. in contrast ,Maggio et al [25]. They reported that normal resistin concentrations were found in their patients, that this was just a reflection of good nutritional and metabolic health and a well-controlled inflammatory response, and that no statistically significant difference was observed between juvenile CKD patients and case-control. The results also showed that Cystatin C levels (p ≤0.01) increased significantly compared to the control group. The results of the current investigation supported a recent work by Waheeb et al. [26]. Who suggested that serum cystatin C is a great endogenous GFR measure since Cys C concentrations tended to be much higher in CKD patients than in healthy people. The body's continual production of cystatin C is unaffected by renal illness, elevated protein catabolism, or dietary factors. Additionally, it does not change with age or growth as creatinine does. Because of its biochemical makeup, cystatin C can be free-filtered in the renal glomeruli before being broken down and reabsorbed by the proximal tubule [26]; in other words, the cystatin C value is an important marker in calculating the GFR because as GFR declines, plasma cystatin C concentrations rise earlier than plasma creatinine, which may be a valuable marker in early detection of impaired renal function in patients with muscle weakness or chronic kidney disease. Cystatin C concentration is regarded as an internal marker of kidney function since the proximal tubules easily filter it and do not depend on age, gender, or body mass [27]. Also, Michele et al. [28]. Found increased cystatin C in dialysis patients. The reason is that cystatin C is a protein with a low molecular weight and a high cationic character, as it is affected by the type of washing membrane and thus hinders the filtration of cystatin C[28]. Compared to the control group, patients with CKD had considerably lower serum albumin levels. This outcome is also in line with the findings of Al-Khafaji et al. [29], who showed that CKD patients have compromised glomerular filtration barriers and high GFRs as a result. Hyper-filtration leads to an increase in intraglomerular pressure, which results in CKD as evidenced by hypoalbuminemia [29]. In the present study, the mean level of CRP of the control group was 5.38 + 0.31mg/L, while that of the patient group was 6.71+ 2.93mg/L. As shown in Table (2), there were no significant changes between the CKD patients and the control group. This result corroborated Lee et al. [30], who looked at CRP levels in certain CKD patients. CRP levels in our study were within the acceptable ranges (6 mg/L). This suggests that there is no correlation between CKD and CRP, and it is comparable to a 2015 study that revealed that CRP is not a stand-alone risk factor for CKD, nor is the risk of developing CKD [30]. In contrast, the study by Mohamed et al. [31] showed that hemodialysis (HD) patients have the highest values of CRP levels versus peritoneal dialysis (PD) or patients receiving conservative treatment. Creatinine is continuously produced in the body and removed via the kidneys' glomerular filtration system [32]. The rate at which the kidneys filter Creatinine can also be used to gauge renal function. Increased serum Creatinine levels may worsen renal function because the kidneys cannot remove Creatinine through urine excretion [32]. in this study, in Table (2) elevated Cystatin C levels may cause the increased Cystatin C to Creatinine ratio, and raised Cystatin C levels have been linked to increased systolic blood pressure and inflammatory markers [33].

According to Table 3 (r = 0.504, p = 0.02 and r = 0.5, p = 0.01 respectively), IL-6-is shown to have significantly positive correlation with Cystatin C and the Cystatin C/ Creatinine ratio; this relationship can be explained by the fact that both are molecules with small molecular weights (less than 55 kilodaltons), as Cystatin C is freely filtered through the glomerulus, which leads to a strong association with biomarkers such as interleukin-6 [34], while non-significant with other parameters. Additionally, there is a highly significant positive association between Resistin and Creatinine as well as between Cystatin C /Creatinine ratio in the group of patients with CKD (r= 0.305, p=0.01, and r= 0.30, p=0.05, respectively) that corresponds to the research[35]. On the other hand, there is a non-significant correlation with other parameters. There is a significant positive correlation between Cystatin C and IL-6- and Cystatin C / Creatinine ratio (r= 0.504, p=0.02 and r= 0.63,p=0.00, respectively), but the correlation is non-significant with other parameters.

Table (4) and figure (1) identify the major biomarkers playing an important role as differentiator factors between the study groups: urea, creatinin, cystatin C, resistin, IL-6, CRP/Albumin*10-4, and CRP/Albumin*104, they are considered as a rapid and accurate laboratory analysis to determine the role of IL-6, Resistin and Cystatin C in pathogenesis of CKD, and correlate their concentrations with clinical and laboratory prognostic factors of the disease.

According to the AUC, sensitivity, and specificity of urea, creatinine, and cystatin C which are 1 for each, that mean 100% of patients are significantly positive patients with clinically elevated cutoff-value more than normal levels (65.5, 1.895, and 1.275) consecutively. In addition, monitoring of the illness's severity is facilitated by the measurement of serum resistin, IL-6, and assessment of the CRP/ Albumin *10-4 and CRP /Albumin *104. In this study found that at an AUC of more than

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0.9, IL-6 and CRP/ Albumin *10-4 were reflect 100% disease-free in apparently healthy participants, and high sensitivity in patients (0.963 and 0.838) respectively.
In turn at more than (0.86) AUC, resistin and CRP /Albumin * 104 were obviously discern between patients as positive instances and participants without disease as negative events were about 82% of patients really diagnosed with investigate the role of these ratios on the progression of the CKD, and 80 % of individuals were accurately designated as healthy.

V. Conclusions

The demographic description of CKD in this study revealed that the patients' group had a higher prevalence of the ages (21-40) than that in the patients of other ages. A slight prevalence in the females over the males was observed weak associations with family history, cigarette smoking, and alcoholism were shown. The presence of high concentrations of IL-6, Resistin, and Cystatin C is associated with chronic kidney disease. The development of the disease is tightly correlated with the studied biochemical characteristics. In CKD patients, a high ratio of cystatin C to creatinine is a sensitive indicator for disease activity association.

VI. Acknowledgement

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VII. References

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TABLE 1 : LISTS THE CLINICAL FEATURES OF CKD PATIENTS.

Variable	Number	Percentage (%)
Total number of patients	80	100
Age a) >20 b)21-40 c)41<	 4 10 66	 5% 12.5% 82.5%
· Gender a) Female b)Male	 46 34	 57.5% 42.5%
· Family History of CKD a) With b)Without	 5 75	 8% 92%
· Smoking a) Smoker b)Non-smoker	 8 72	15% 85%
Alcoholism Non-alcoholism	3 77	5% 95%

TABLE 2: COMPARISON BETWEEN PATIENTS AND CONTROL GROUPS REGARDING IL-6-,RESISTIN ,CYSTATIN C, CREATININE AND THE RATIO OF CYSTATIN C TO CREATININE.

Parameters	Groups	Mean + SD	p-value
IL-6- ng/ L	Patient Group Control Group	378.61 ± 99.89 70.01 ±21.52	.000 **
Resistin ng/ L	Patient Group Control Group	2031.03 ± 507.75 373.20 ± 25.08	.000 **
Cystatin C mg/L	Patient Group Control Group	2.17 ± 0.33 0.72 ± 0.07	.000 **
Albumin g/dl	Patient Group Control Group	1.43 ± 0.53 4.38 ± 0.31	.000 **
CRP mg / L	Patient Group Control Group	6.71± 2.93 5.38 ± 0.31	0. 16 NS
Creatinine mg / dl	Patient Group Control Group	8.34 ± 2.16 0.86 ± 0.11	.000 **
CRP /Albumin×10^4	Patient Group Control Group	20203.11 ± 6920 19006.8 ± 7013.19	0.320 NS
Cystatin C /Creatinine ×10	Patient Group Control Group	8.11 ± 1.96 2.92 ± 0.44	.000 **

** refer to high significant differences between the groups at (P≤0.01)

NS refer to non significant differences between the groups at (p≤ 0.05)

TABLE 3: CORRELATION AMONG IL-6 ,RESISTIN ,CYSTATINC, CREATININE AND CYSTATIN C/ CREATININE RATIO UNDER STUDY IN CKD PATIENTS.

Parameters Under Study	IL-6-		Resistin		CystatinC	
	R	P	R	P	R	P
IL-6-	1.00		0.17	0.12	0.504*	0.02
Resistin	0.17	0.12	1.00		0.30	0.19
CystatinC	0.504*	0.02	0.30	0.19	1.00	
Albumin	-0.01	0.96	-0.06	0.62	-0.14	0.56
CRP	0.04	0.72	0.09	0.41	0.02	0.93

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Creatinine	0.10	0.39	0.305**	0.01	0.09	0.71
CRP / Albumin	0.03	0.76	0.14	0.20	0.12	0.62
Cystatin C/ Creatinine	0.50**	0.01	0.30*	0.05	0.63**	0.00

**. Correlation is significant at (P≤ 0.01).

*. Correlation is significant at (P≤ 0.05) .

TABLE 4: ROC ANALYSIS

Variables	Area Under the Curve (AUC)	Cutoff-Value	Sensitivity	Specificity	Asymptotic Sig.[b]
U	1.000	65.5	1	1	0.000
Cr	1.000	1.895	1	1	0.000
Cystatin C	1.000	1.275	1	1	0.000
RESIS	0.884	436	0.825	0.8	0.000
IL6	0.983	112.3	0.963	1	0.000
CRP/ Albumin *10^{-4}	0.951	0.0001	0.838	1	0.000
CRP /Albumin * 10^4	0.863	12465	0.813	0.8	0.000
b. Null hypothesis: true area = 0.5					

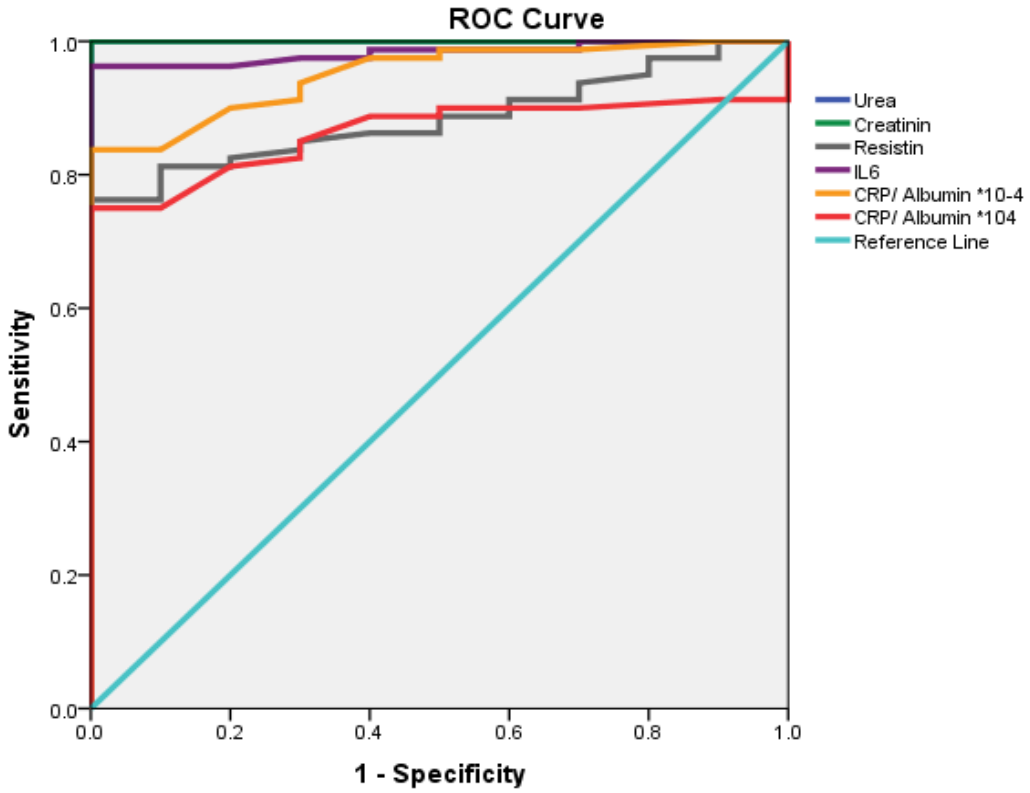

Fig (1): ROC Curve

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