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Evaluation of IL-6 and IL-30 Serum level in Addition To Some Biochemical Markers in Iraqi Patients with Chronic Renal Failure

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Abstract: Chronic kidney disease CKD is defined as the presence of structural or functional abnormalities of the kidneys for more than three months, with health implications. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD should be classified according to its cause and category of glomerular filtration rate (GFR) and albuminuria, which are factors that enable the identification of the risk of adverse outcomes, such as progressive CKD, end-stage renal disease, acute kidney injury, all-cause mortality and cardiovascular mortality. We aimed to evaluated (IL-6 and IL-30) in Iraqi patients with chronic renal failure and assess some biochemical parameters include (urea, creatinine, protein,albumin, calcium and vitamin D).This study included 88 cases and classified as 44 patients with chronic renal failure, these patients with age range (18 to 65) years who were admitted to the AL-Kindi Dialysis Center during the period from December 2024 to March 2025 Regarding biochemical parameters, it was observed that serum urea (S.urea), serum creatinine (S.creatinine) ,serum potassium (S. K) were increased in chronic renal cases and decrease in Serum calcium (S. Ca,),Serum sodium (S. Na) and serum vitamin D (S. vit D) in comparison with healthy control group. **The results showed that male patients constituted 58.1% while the controls were 41.9% out of a total of 43 individuals assigned to the patients' group. The mean age of the males was 51.16±13.6 and 51.44±11.0 for the patients and the controls, respectively. Moreover, out of a total of 53 females, there was 43.3% patients and 56.6% controls; their mean age was 49.13±12.7 and 42.47±14.0. An Independent-Samples Mann-Whitney U Test was applied to compare the medians serum levels of IL-6 and IL-30 in patients and controls. also results show highly statistically significant difference (p=0.005) between patients and controls when IL-6 was considered while no difference obtained when IL-30 was taken into consideration.Highly significant elevated of pro-inflammatory cytokines which include IL-6 in chronic renal diseases indicated these cytokines participate in the pathophysiology of reduced renal function and the role of these cytokines as principle mediators of inflammatory reaction in renal damage and these cytokines could be potential therapeutic targets.

Keywords: Chronic renal disease, Biochemical tests, IL-30, IL-6.

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Introduction

Chronic kidney disease(CKD)or Chronic Renal Failure (CRF) has been defined as kidney damage or an estimated GFR (eGFR) less than 60ml/min/1.73m2 persisting for three months or more regardless of the cause. The kidney disease improving global outcome (KDIGO) classification system recommends that kidney function be estimated by glomerular filtration rate (GFR) calculation from serum creatinine level through a special equation. More than two million

worldwide patients with CKD Progress to end stage renal disease and need dialysis or renal transplantation (1.(

It is a progressive loss of kidney function ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates (2). Worldwide, CKD accounted for three million and over two million of life-years lost in 2012 (3). Various symptoms and disorders including water electrolyte balance disorders, metabolic acidosis, anemia, hypertension, hypophosphatemia with bone disease (4). Risk factor for kidney disease include race, gender, age, and family history are highly important. Moreover, smoking, hypertension, and diabetes mellitus, obesity can also lead to kidney disease (5,6). CKD presented with elevated blood urea and creatinine are found during routine examination (7,8). Chronic inflammation is prevalent in patients with chronic renal failure (9). Numerous studies have demonstrated that chronic inflammation may contribute to the morbidity and mortality among dialysis patients (10). Indeed, deterioration of renal function in uremia increases risk to infection and various abnormalities of the immune system (11) In addition, the repeated dialysis treatments in patients lead to leucocyte activation and consequently the production of cytokines. (12 .(

Interleukin 6 (IL-6) is one of the main modifiers of acute phase response, which is observed to be high in patients with end-stage disease of Dialysis (ESRD) and is a powerful predictor of noticing the disease outcome. Moreover, it plays an important role in the relationship between inflammation, Malnutrition, and cardiovascular diseases in patients who have blood Hemodialysis (HD) (13,14). Interleukin-6 (IL-6) is a proinflammatory cytokine that was first identified as a B-cell stimulatory factor, IL-6 has many functions in the regulation and coordination of the immune system, metabolism, and nervous system. It plays a role in the body's defense against infection, in many regenerative processes (15). The elevated plasma IL-6 level is commonly observed in CKD patients (16).it has been suggested that Interleukin-6 accelerates the progression of CKD not only by aggravating kidney injury but also by initiating its complications, especially the chronic vascular disease (CVD). It is demonstrated that IL-6 initiates the endothelial injury mainly via reducing endothelial nitric oxide synthase (eNOS) and adiponectin (an anti-atherogenic adipokine) expression. (17). And interleukin-30 (IL-30)), IL-30 plays an anti-inflammatory role,it wasconcluded that male and aging are predisposing factors to chronic renal disease, and elevated levels of IL-6 in patients with CKD reflect the potential role of IL-6 in the progression of chronic renal disease.

Aims of the study

Evaluation of IL-6 and IL-30 Serum level and Inflammatory Biomarkers in Patients Infected with Chronic Kidney Disease

Materials and Methods:

A-Sample collection

The study included 44 patients with CKD were included in the study patients with age group (15-65) years who were admitted to AL-Kindi Dialysis Center in Baghdad city and 44 healthy persons were used as a control sample and paired with patients based on sex and age. Among them, 23 were females and 25 were males. 5 mL of venous blood samples were taken from

both patients and controls. The blood samples were incubated at room temperature for 30 minutes, followed by centrifugation at 3000 revolutions per minute for 5 minutes. The serum was removed, aliquoted and stored at -20 °C until time of assay. Then serum were used for detection of biochemical parameters included (Urea, creatinine, sodium, potassium, Calcium Protein, Albumin and Vitamin D) by the enzymatic colorimetric method (using multi chemical fully automated chemistry analyzer) (Abbott/UsA).

addition serum concentrations of IL-6 and IL-30 were measured by ELISA(Enzyme Linked Immuno Sorbant Assay) test (Human reader/Germany).

B-Statical analysis:

In this study Chi-square test was used to detect the significances between variables. All the statistical analysis was done by SPSS program (version-20). Data was presented as Mean ± Stander error. P-value was considered significant less than < 0.05.

Results:

current study involved 88 samples divided into two groups (44 chronic renal failure and 44 healthy apparent controls). Age of the study population ranged from(18-65) years. Table (1) shows the study group were categorized according to gender in chronic patients group 23 (43.4%) female whereas 25 (58.1%) were male.

The results showed that male patients constituted 25(58.1%) while the controls were 41.9% out of a total of 43 individuals assigned to the patients' group. The mean age of the males was 51.16±13.6 and 51.44±11.0 for the patients and the controls, respectively. Moreover, out of a total of 23 females, there was 43.3% patients and 56.6% controls; their mean age was 49.13±12.7 and 42.47±14.0 as per order as Table (1).

Table (1): Distribution of study groups according to gender.

Gender	Patients	Controls	Total
	Frequency (%)		
Male	25 (58.1)	18 (41.9)	43 (100)
Mean age±SD	51.16±13.6	51.44±11.0	
Female	23 (43.4)	30 (56.6)	53 (100)
Mean age±SD	49.13±12.7	42.47±14.0	
Total	48 (50)	48 (50)	96 (100)

Independent-Samples Mann-Whitney U Test was applied to compare the mean concentrations of the variables listed in Table….. in the patients and controls groups. The results are indicated by median (interquartile range) and showed very highly statistically significant difference ($p \leq 0.001$) when urea, K, Ca, protein, and vitamin D values of the patients and controls were compared. Furthermore, highly statistically significant difference ($p=0.007$) was noted when the values of albumin were compared, finally, there was no statistically significant difference ($p=0.38$) when the folds of VDR gene expression were compared.

Table (2): Level of Biochemical tests of patients and control group.

Variable	Normal value	Group	Median (IQR)	P-value
Urea (mg/dl)	**(17-43)**	Patients	149 (48)	≤0.001***
		Controls	31 (12)	
K (mmol/L)	**(3.6-5.2)**	Patients	5.3 (1.28)	≤0.001***
		Controls	4.3 (1.2)	
Ca (mg/dl)	**(6.8-10.3)**	Patients	8.28 (1.4)	≤0.001***
		Controls	9.4 (1.4)	
Protein (mg/dl)	**(0-20)**	Patients	6.3 (0.8)	≤0.001***
		Controls	6.8 (0.85)	
Albumin (mg/dl)	**(3.4-5.4)**	Patients	3.8 (0.6)	0.007**
		Controls	4.1 (1.28)	
Vitamin D (mg/dl)	**(30-50)**	Patients	8.0 (9.8)	≤0.001***
		Controls	21.1 (17.2)	
Fold of VDR expression		Patients	1.2 (1.43)	0.38
		Controls	1.06 (1.01)	

*****very highly statistically significant at p≤0.001, **highly statistically significant at p≤0.01**

K(potassium),Ca(calcium) An independent samples t test was applied to find the difference between the mean serum concentrations of creatinine and Na, the mean serum concentration of creatinine was 8.08 ± 2.8 while that of the controls was 0.82 ± 0.3; Sodium mean concentration was 135.2 ± 4.3 and 141.7 ± 5.2 for the patients and controls, respectively. The results indicated very highly statistically significant difference (p≤0.001) when the patients and controls values of the two variables were compared as Table(3).

Table (3): Level of (Creatinine and Sodium) of patients and control group.

Variable	Normal value	Group	Mean ± SD	P-value
Creatinine (mg/dl)	**(0.7-1.3)**	Patients	8.08 ± 2.8	≤0.001***
		Controls	0.82 ± 0.3	
Na (mmol/L)	**(135-145)**	Patients	135.2 ± 4.3	≤0.001***
		Controls	141.7 ± 5.2	

*****very highly statistically significant difference at p≤0.001.**

An Independent-Samples Mann-Whitney U Test was applied to compare the medians serum levels of IL-6 and IL-30 in patients and controls. The results showed highly statistically significant difference (p=0.005) between patients and controls when IL-6 was considered while no difference obtained when IL-30 was taken into consideration as Table(4).

Table (4): Levels of cytokines between patients and control group.

Variable	Median (IQR)		P value
	Patients group (n=44)	Controls group (n=44)	
IL-6	2.88 (3.57)	1.93 (2.20)	0.005**
IL-30	6.93 (9.27)	6.45 (4.20)	0.231

****Highly significant at p≤0.01.**

Discussion

Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world population. It is defined on the basis of an estimated glomerular filtration rate (eGFR) and values less than 60 mL/min/1.73 m2 are considered the threshold for CKD (2). Many are undiagnosed and asymptomatic. Only in the UK there are approximately 1 million undiagnosed CKD patients. CKD results in changes in vitamin D metabolism, calcium and phosphate homeostasis and bone metabolism. This leads to CKD metabolic bone disease (CKD–MBD)(1).

Chronic kidney disease (CKD) is a major social health problem. Healthy kidneys are important for the efficient

regulation of metabolism. However, there is an ever increasing population of patients suffering from both acute and chronic kidney diseases that disrupt this homeostasis. In the current study demonstrated that highest prevalence (60%) of chronic renal failure within age group (15-65) years similar results were found by other Study (18) which confirmed that a high prevalence of CKD in the elderly less than (65 years),this results shown some compatibility to other studies. (19) which reported that age group more than 60 years constituted (25.8%) from all cases of CKD patients. Regarding data of the National Institutes of Health in the United State (21) CKD is more common in people aged 65 years or older (38%) than in people aged 45–64 years (12%) or 18–44 years (6%) and those results were unlike with the current study. this variation due to the sample size, geographic distribution, life style different from country to country.

In concordance to other studies (20, 22, 24) our study showed a higher prevalence of CKD in female registered 23 (43.4%) compared with male recorded 25 (58.1%)). So the female gender was the strongest risk factor for CKD in the current study. It may be a result of the difference between women and men in glomerular structure, glomerular haemodynamics, muscle mass, and the hormone metabolism, Additionally, these days the higher CKD prevalence in women might be caused by lower physical activity and high prevalence of cardiometabolic risk factor (25).

In addition, the current observation appeared that mean of Serum Urea, creatinine, sodium, potassium, Calcium Protein, Albumin and Vitamin D was significant low among CKD in comparing with control group. This results homogenous with other studies (26, 27). In Iraqi, in 2018 (29) which identified there was decrease in the concentration of total Urea, creatinine, sodium, potassium, Calcium Protein, Albumin and Vitamin D in serum of CKD patients group in comparing with control group. These results agreement with our results. In contrast to the present study, previous studies (28,29) which demonstrated that significant increases of Serum Ca in CKD.

This variation in results may be due to the lack of a standardized reference range for serum calcium, which is instead established by individual laboratories or commercial suppliers of the assays or analyzers. While guidelines exist for determining normal ranges including subject selection, sample size, and biologic variables in addition the normal ranges may vary with age, gender, or ethnicity and are often dynamic in relationship to meals or time of day. Serum calcium is particularly challenging since it is the ionized component, rather than the total (30).

As shown in Table (4), the results indicated there was a significant increase of IL-6 (2.88 (3.57)) in all patients with chronic renal compare with healthy groups. The current results were in line with Iraqi study by (31) who indicated there was a significantly an increased levels of IL-6 (26.26 ±1.48) in chronic renal patients on hemodialysis when compared with control group (13.02 ±0.34) (31) . Furthermore,(32) found that higher sera levels of IL-6 presented in patients CKD with an average of 177.71 pg / ml compared to 129.46 pg / ml of control group , another study indicated low concentration of IL-6 serum level in the patients (28.037pg/ml) significantly at ($P < 0.000$), when compared with those of healthy (96.1pg/ml) and concluded

the hemodialysis patients display decrease in the concentration of IL-6 serum level and this condition referred to susceptibility to infection by various disease due to the anti-inflammatory state (33) .

The IL-6 family of cytokines are involved in a diverse range of physiological functions. In relation to kidney disease, their involvement is no less diverse. Evidence from both preclinical and clinical sources show that IL-6 cytokine family members can play either a deleterious or protective role in response to kidney disease. Interleukin-6 (IL-6) was discovered in 1986 as a B cell stimulatory factor initiating IgG production. Later, it was demonstrated to be a multifunctional cytokine that regulates numerous biological processes including the organ development, acute-phase responses, inflammation, and immune responses (34). Interleukin-6 (IL-6) is a pleiotropic cytokine that not only regulates the immune and inflammatory response but also affects hematopoiesis, metabolism, and organ development. IL-6 can simultaneously elicit distinct or even contradictory physiopathological processes, which is likely discriminated by the cascades of signaling pathway, termed classic and trans-signaling. Besides playing several important physiological roles, dysregulated IL-6 has been demonstrated to underlie a number of autoimmune and inflammatory diseases, metabolic abnormalities, and malignancies(35). While IL-30 regulates T cells to mitigate inflammation-induced acute and chronic liver damage(36).

Conclusions

It was concluded that male, aging are predisposing factors to chronic renal disease. An elevated mean serum levels of IL-6 in chronic kidney disease patients. patients reflect the potential role of IL-6in the progression of chronic renal disease. So, it is considered as an indicator sign of decreased kidney function. Moreover, the measurement of IL-6 and IL-30 and conventional renal biomarkers holds promise for improving clinical management and outcomes in patients with chronic kidney disease.

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