Elevation of IL-17 in Chronic kidney Failure in Iraqi Patient

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Abstract—**One of the most significant social health issues is chronic kidney disease (CKD). The Republic Ministry of Health/Environment reported that 6,879 persons died in 2015 from renal failure, placing chronic kidney disease (CKD) at number five on the list of Iraq's most dangerous diseases.**

Materials and Methods: This study included 60 cases that were classified as 30 patients with chronic renal failure; these patients, age range 30 – 59 years old were admitted from the Al-Karama Teaching Hospital, Baghdad province, during the period from December 2022 to January 2023 which they compared with 30 samples of healthy controls. For determining the IL-17 levels, the researchers employed Enzyme-linked immunosorbent assay (ELISA).

Results: It was found that most of the people who suffer from CKD failure within the age group (40- 49) years that account (60%), and most of these patients were females that constituted (59%). IL-17 serum level increases significantly (27.28 ±1.50) in chronic renal patients compared to the control group (13.02 ±0.34).

Conclusion: Highly significant elevated pro-inflammatory cytokines (IL-17) in chronic renal diseases indicate these cytokines participate in the pathophysiology of reduced renal function and the role of this cytokine as principal mediators of inflammatory reaction in renal damage.

Index Terms— **IL17, Urea, Creatinine, Albumin, Renal failure.**

I. INTRODUCTION

Chronic Renal Failure (CRF), also known as chronic kidney disease (CKD), is renal impairment or a GFR below 60 ml/min that lasts three months or longer [1]. Renal failure is a gradual but continuous reduction in kidney function that requires dialysis or transplantation [2].

Infectious pathogens and pathogenic immune responses often target the kidneys in both systemic and organ-specific autoimmunity. As stated by the National Institutes of Health, the Kidney is an organ that is especially vulnerable to harm resulting from autoimmune disorders and infections. Inflammation of the kidneys provides a defence against microbial infections. However, kidney injury may result from untreated inflammation if left unchecked. Autoimmunity leads to renal failure, and dysregulated IL-17 response is related to it. IL-17 is a proinflammatory cytokine that is essential for defence against external infections. Approximately 14% of the US population (∼20 million) suffer from chronic renal disorders. In 2012, CKD caused the loss of three million and more than two million life-years worldwide [3-5]. Chronic kidney disease (CKD) is more common in industrialised countries than in other parts of the globe because people there tend to live longer and lead unhealthy lives [6]. High blood pressure, type 2 diabetes, obesity, and cardiovascular disease are frequent in industrialised nations. These conditions are known as chronic renal disease risk factors [7].

Important kidney disease risk factors include age, race, gender, and race, as well as family history. Additionally, hypertension, obesity, smoking, and smoking can all contribute to the development of renal disease. The pathophysiology of CKD is intricate and often affected by the interplay of external and internal variables. Cytokines are among the endogenous factors generated mostly by macrophages [8].

Regardless of the initiating reason, CKD development is accompanied by a much-increased amount of inflammation, which activates the immune system. Inflammation leads to the development of acute kidney damage and post-renal acute kidney injury. Additionally, it contributes to the progression of atherosclerosis, resulting in CKD and a decline in kidney function. The severity of CKD is related to the inflammatory response amount, which rises linearly as renal failure progresses [9].

Activated blood macrophages generate cytokines, which serve as critical mediators in regulating the magnitude of the immune response and, consequently, in facilitating the disease's progression [10]. Pathophysiological pro- and anti-inflammatory cytokines determine inflammation outcomes. Cytokines impact acute and chronic renal disorders [11].

Many cytokines are known to promote inflammation, including interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17 (IL-17), and tumour necrosis factor-α [12]. Age, obesity, type 2 diabetes, and recurring infections are risk factors for chronic inflammation

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[13].
The cytokine IL-17 is specific to Th17 (T helper 17) cells. Its function in host defence against infections, autoimmunity, and allergy disorders has been well investigated [14]. Nevertheless, as time passed, it became evident that IL-17 is involved in a far greater number of physiological and pathological conditions than first suggested [13].
The cloning of IL-17 (IL-17A) occurred in 1993 [14]. Six cytokines comprise the IL-17 family: IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. Five receptor subtypes comprise the IL-17R family: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [15].
Chronic inflammation has been connected to IL-17 in several illnesses, including kidney disorders. The blood levels of IL-17 in patients with autoimmune renal disorders are significantly elevated, and a direct correlation exists between IL-17 levels and the activity of the disease [15]. Numerous kidney cells, including podocytes, mesangial cells, and renal endothelium cells, carry IL-17 receptors, which trigger an inflammatory response that damages and disrupts nephron function [13].
In addition, IL-17 receptors activate pathways that promote fibrosis and lead to the deterioration of organ function. Figure (1) illustrates how these interactions lead to autoimmune kidney disorders [16]. Insufficient or ineffective therapy may lead to the development of chronic kidney disease (CKD), which increases the likelihood of cancer via many mechanisms [17].

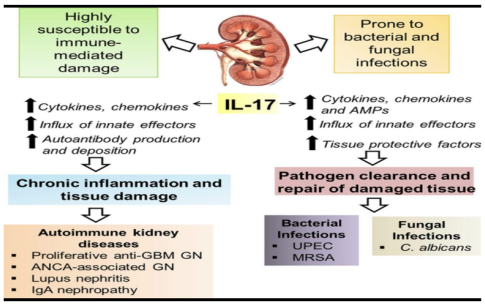

Figure (1): IL-17 renal activities in kidney diseases

When kidney damage progresses slowly, the indications and manifestations of chronic renal illness emerge gradually. Electrolyte imbalances, fluid retention, and other complications may arise from renal failure [3]. The following symptoms of loss of kidney function might vary depending on how severe it is: nausea, vomiting, lack of appetite, Weakness and exhaustion. Symptoms include shortness of breath if fluid builds up in the lungs, chest pain if fluid builds up around the heart's lining, difficulty sleeping, infrequent urination, decreased mental acuity, muscle cramping, foot swelling, dry, itchy skin, and hypertension. Kidney disease symptoms and signs are often ambiguous. This indicates that other diseases may cause them. Our kidneys can compensate for reduced function, so we may not notice signs and symptoms until permanent damage has occurred. The development of kidney failure due to chronic renal illness may be averted with the help of early identification [18].
More people die from kidney disease than from breast or prostate cancer combined [19]. The under-recognised public health crisis is at hand. Around 90% of individuals afflicted with kidney disease are unaware of their condition. Furthermore, severe kidney disease is unknown to two out of every five adults. The incidence of kidney disease is comparatively higher among women (14% vs. 12%) [20]. In the United States, kidney disease is the primary cause of mortality [21, 22]. One in every three adults diagnosed with diabetes, and one in every five adults with hypertension may be afflicted with renal disease [20]. COVID-19 targets people with kidney illness, kidney transplant recipients, and high-risk kidney disease patients [19, 21].
Early diagnosis may avoid kidney disease. There are two affordable, rapid, and basic kidney disease tests: A kidney damage urine albumin-creatinine ratio (ACR) test evaluates urine albumin. Kidney damage causes the protein to be eliminated in the urine rather than staying in the blood. In addition, the blood test creatinine determines the glomerular filtration rate (GFR), which indicates the kidneys' capacity to eliminate waste from the blood [22]. High IL-17 levels in Iraqi patients with chronic renal failure are the focus of the present work

II. MATERIAL AND METHODS

A. Blood Sampling and Collecting

The blood samples were gathered in Al-Karama hospital in Baghdad province between the period from December 2022 to January 2023 with an age range of 30 – 59 years old, with 60 samples classified as 30 patients with chronic renal failure and compared with 30 healthy controls.
All patients who are in the study sample suffer from acute kidney failure with high levels of Urea, Creatinine, Albumin, and urinary tract infection.
The blood samples were obtained throughout the time frame of 7:30 to 8:30 in the morning. Before centrifugation at 3000 x g for 10 minutes to separate the tubes from the cells, they were stored at -20 °C until testing. The samples were then kept in a cool atmosphere for 30 minutes.

B. Measuring of Serum Biochemical Tests

An autoanalyser assessed kidney function by conducting standard laboratory tests, including blood urea, serum creatinine, serum uric acid, and urine albumin.

C. Measuring of Serum Interleukins Il-17

The Enzyme-Linked Immunosorbent Assay Kit (ELISA) was used to measure the blood levels of IL-17. My bio-source company provided the ELISA kits based in the United States.

III. RESULT

A. Age

The present investigation included 60 samples, separated into two groups (30 chronic renal failure and 30 healthy apparent controls). The research population's age varied from 27 to 78 years. Table (1) shows Chronic patients aged (40-49) had the highest prevalence of 18 (60%) when compared with other groups, while 8 (26%) of patients within the age group (30-39) and only 4 (13%) within (50-59). There are highly significant differences between the incidences of the different age groups

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among chronic renal patients (P<0.001).

Table (1): Demographic of study groups according to the Age

The age range of patients	NO (%)
30-39	8 (26%)
40-49	18 (60%)
50-59	4 (13%)
Total (%)	30 (100%)
P-value	0.0007**

B. Gender

In the chronic patient group, there were 17 females (59% of the total) and 13 males (or 41% of the total), as shown in Table 2. A statistically insignificant difference did not exist between the sexes (p=0.107).

Table (2): Demographic of study groups according to the gender

Gender of patients	NO (%)
Male	13 (41%)
Female	17(59%)
Total (%)	30 (100%)
P-value	0.0001**

C. Il-17

As shown in Table (3), the Result of IL-17 between chronic renal patients and a control group indicated that the mean for chronic was (27.28 ±1.50) and the mean for control (13.02± 0.34). The results revealed a highly significant difference at (p=0.0001).

Table (3): Levels of cytokines between chronic renal patients and control group.

Studied Groups (Il-17)	Mean ± SE
Chronic group	27.28 ±1.50
Control group	13.02 ±0.34
P-value	0.0001**
**** (P≤0.01) Highly Significant** **SE=Standard Error**	

IV. DISCUSSION

One of the most significant social health issues is CKD. The current study demonstrated that the highest prevalence (60%) of chronic renal failure within the age group (40-60) year agrees with the results found by other Stud[23]ies [24]. Also, in this study, the CKD prevalence in the age group 61-78 was 13%. These results agree with other studies. Which reported that an age group of more than 60 years constituted (25%) of CKD patients [24].

The variation between studies of CKD is due to the sample size, geographic distribution, lifestyle, and degree of education for people different from country to country. Women had 59% of CKD, compared to 41% for males, making them the biggest risk factor for CKD in this research. This could be because of gender differences in hormone metabolism, glomerular shape and hemodynamics, muscle mass, and other physiological factors. Additionally, repeated urinary tract infections occur more in females than in males. Pregnancy and childbirth may cause a higher rate of infection in women than in males [25].

Compared to the control group, individuals with CKD had a much greater level of IL-17, according to the present study. Inflammatory infections in CKD patients result from increased T cell IL-17 synthesis and CRP and TNF-α production following antigen exposure. These findings align with previous studies [26].

CONCLUSION

Pro-inflammatory cytokines (IL-17) were found to be significantly elevated in chronic renal diseases, indicating a possible role for these cytokines in the pathophysiology of compromised renal function. Furthermore, these cytokines are major mediators of inflammatory reactions in renal damage.

REFERENCES

1. *A. S. Levey, P. E. De Jong, J. Coresh, M. El Nahas, B. C. Astor, K. Matsushita, et al., "The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report," Kidney international, vol. 80, pp. 17-28, 2011.*
2. *S. L. Martínez-Hernández, M. H. Muñoz-Ortega, M. E. Ávila-Blanco, M. Y. Medina-Pizaño, and J. Ventura-Juárez, "Novel Approaches in Chronic Renal Failure without Renal Replacement Therapy: A Review," Biomedicines, vol. 11, p. 2828, 2023.*
3. *A. C. Webster, E. V. Nagler, R. L. Morton, and P. Masson, "Chronic kidney disease," The lancet, vol. 389, pp. 1238-1252, 2017.*
4. *A. L. Flores-Mireles, J. N. Walker, M. Caparon, and S. J. Hultgren, "Urinary tract infections: epidemiology, mechanisms of infection and treatment options," Nature reviews microbiology, vol. 13, pp. 269-284, 2015.*
5. *T. Mustafa and H. Mohammed, "Cytotoxicity Effect of Laserpitium Carduchorum Extract in Mcf-7 Human Breast Cancer Cells Via Cell Cycle Arrest and Induction if Apoptosis," International Journal of Psychosocial Rehabilitation, vol. 24, pp. 1620-1628, 02/18 2020.*
6. *A. C. Ricardo, C. A. Anderson, W. Yang, X. Zhang, M. J. Fischer, L. M. Dember, et al., "Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study," American Journal of Kidney Diseases, vol. 65, pp. 412-424, 2015.*
7. *A. J. Bleyer, L. R. Shemanski, G. L. Burke, K. J. Hansen, and R. G. Appel, "Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population," Kidney international, vol. 57, pp. 2072-2079, 2000.*

DOI: http://doi.org/10.24086/biohs2024/paper.1406

8. *H. Lee, M. B. Fessler, P. Qu, J. Heymann, and J. B. Kopp, "Macrophage polarization in innate immune responses contributing to pathogenesis of chronic kidney disease," BMC nephrology, vol. 21, pp. 1-13, 2020.*

9. *M.-G. Kim, S. C. Kim, Y. S. Ko, H. Y. Lee, S.-K. Jo, and W. Cho, "The role of M2 macrophages in the progression of chronic kidney disease following acute kidney injury," PloS one, vol. 10, p. e0143961, 2015.*

10. *J. J. Carrero, S. H. Park, J. Axelsson, B. Lindholm, and P. Stenvinkel, "Progress in Uremic Toxin Research: Cytokines, Atherogenesis, and Hypercatabolism in Chronic Kidney Disease: A Dreadful Triad," in Seminars in dialysis, 2009, pp. 381-386.*

11. *L. Koelman, O. Pivovarova-Ramich, A. F. Pfeiffer, T. Grune, and K. Aleksandrova, "Cytokines for evaluation of chronic inflammatory status in ageing research: reliability and phenotypic characterisation," Immunity & Ageing, vol. 16, pp. 1-12, 2019.*

12. *K. F. Al-Rawi, H. H. Ali, M. A. Guma, B. J. M. Aldahham, S. F. T. Alaaraji, O. Al-Ani, et al., "Relationship Between IL-2, IL-17 Concentrations, and Serum Creatinine Levels in Men with Chronic Kidney Diseases," Reports of Biochemistry & Molecular Biology, vol. 10, p. 664, 2022.*

13. *O. M. Akchurin and F. Kaskel, "Update on inflammation in chronic kidney disease," Blood purification, vol. 39, pp. 84-92, 2015.*

14. *K. J. Jager, C. Kovesdy, R. Langham, M. Rosenberg, V. Jha, and C. Zoccali, "A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases," vol. 34, ed: Oxford University Press, 2019, pp. 1803-1805.*

15. *S. L. Gaffen, R. Jain, A. V. Garg, and D. J. Cua, "The IL-23–IL-17 immune axis: from mechanisms to therapeutic testing," Nature reviews immunology, vol. 14, pp. 585-600, 2014.*

16. *P. S. Biswas, "IL-17 in renal immunity and autoimmunity," The Journal of Immunology, vol. 201, pp. 3153-3159, 2018.*

17. *X. Peng, Z. Xiao, J. Zhang, Y. Li, Y. Dong, and J. Du, "IL-17A produced by both γδ T and Th17 cells promotes renal fibrosis via RANTES-mediated leukocyte infiltration after renal obstruction," The Journal of pathology, vol. 235, pp. 79-89, 2015.*

18. *J. Scheller, A. Chalaris, D. Schmidt-Arras, and S. Rose-John, "The pro- and anti-inflammatory properties of the cytokine interleukin-6," Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, vol. 1813, pp. 878-888, 2011.*

19. *S. L. Murphy, J. Xu, K. D. Kochanek, E. Arias, and B. Tejada-Vera, "Deaths: final data for 2018," 2021.*

20. *K. Charles, M. J. Lewis, E. Montgomery, and M. Reid, "The 2021 Chronic Kidney Disease Epidemiology Collaboration Race-Free Estimated Glomerular Filtration Rate Equations in Kidney Disease: Leading the Way in Ending Disparities," Health Equity, vol. 8, pp. 39-45, 2024.*

21. *A. M. Hussein, H. A. Majeed, N. R. Majeed, N. H. Ali, D. A. Saeed, and N. A. Ali, "An Overview of Signs and Symptoms to Determine Coronavirus and Omicron Patients in Primary Care and Hospitals," Cihan University-Erbil Scientific Journal, vol. 8, pp. 8-17, 2024.*

22. *L. Zsom, M. Zsom, S. A. Salim, and T. Fülöp, "Estimated glomerular filtration rate in chronic kidney disease: a critical review of estimate-based predictions of individual outcomes in kidney disease," Toxins, vol. 14, p. 127, 2022.*

23. *M. Mallappallil, E. A. Friedman, B. G. Delano, S. I. McFarlane, and M. O. Salifu, "Chronic kidney disease in the elderly: evaluation and management," Clinical Practice (London, England), vol. 11, p. 525, 2014.*

24. *K. L. Johansen, G. M. Chertow, R. N. Foley, D. T. Gilbertson, C. A. Herzog, A. Ishani, et al., "US renal data system 2020 annual data report: epidemiology of kidney disease in the United States," American journal of kidney diseases, vol. 77, pp. A7-A8, 2021.*

25. *S. R. Silbiger and J. Neugarten, "The role of gender in the progression of renal disease," Advances in renal replacement therapy, vol. 10, pp. 3-14, 2003.*

26. *Z.-y. Li, Y. Zheng, Y. Chen, M. Pan, S.-b. Zheng, W. Huang, et al., "Brazilin ameliorates diabetic nephropathy and inflammation in db/db mice," Inflammation, vol. 40, pp. 1365-1374, 2017.*

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