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Evaluation of Some Immune Markers in Patients Undergo Hemodialysis.

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Abstract

Objective: The aim of the current study to evaluate serum levels of (IL-2 , IL-4 and IL-6) in chronic renal disease patient before and after hemodialysis.

Material and Methods: Fifty patients with renal failure; Aged 40-70 years were enrolled in the study were collected from Al-Batool Teaching Hospital in Al-Kut, Wasit , Iraq. For comparison, thirty normal persons were examined as a control for all parameters of the patients group. Interleukins IL-2, IL-4 and IL-6 were measured by using ELISA technique.

Results: There was a significant difference in the mean of IL-6 when compare between patients pre and post dialysis (13.72 ± 0.74 vs. 40.14 ± 1.87 pg/ml respectively, $p < 0.0001$), but there was no significant difference when compare between control (10.64 ± 0.78 pg/ml) and pre-dialysis patients ($p>0.05$). There was a significant difference in IL-2 levels when compare between control and pre-dialysis patients group (2.08 ± 0.10 vs. 3.18 ± 0.08 pg/ml respectively, $p < 0.0001$), as well as, there was a significant difference when compare between pre and post dialysis patients (3.71 ± 0.11 pg/ml). There was a significant difference between control and post dialysis patients There was a significant difference in IL-4 levels when compare between control and both pre and post patients groups (1010.47 ± 22.16 mg/dl vs. (1221.50 ± 21.98 & 1673.04 ± 56.19 mg/dl) respectively, $p < 0.0001$) and there was a significant difference when compare between pre and post dialysis patients groups.

Conclusion: Both IL-2 and IL-6 significantly elevated when compare patient's pre and post dialysis. IL-2 was significantly increase in patients when compare to control.

Keywords: IL-2,IL-4, IL-6, ESRD

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تقييم بعض المؤشرات المناعية لدى المرضى الذين يخضعون لغسيل الكلى

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المستخلص

الهدف: تهدف الدراسة الحالية الى تقييم مستويات (انترلوكين-2،انترلوكين-4،انترلوكين -6) لدى مرضى الكلى المزمن قبل وبعد غسيل الكلى.

المواد وطرق العمل: خمسون مريضا يعانون من الفشل الكلوي . تم جمع المشاركين في الدراسة الذين تتراوح اعمارهم بين(40-70 سنة) من مستشفى البتول التعليمي في الكوت، واسط، العراق . للمقارنة ، تم فحص ثلاثين شخصا طبيعيا كعنصر تحكم لجميع معايير مجموعة المرضى. تم قياس الانترلوكينات (انترلوكين-2،انترلوكين-4،انترلوكين -6) باستخدام تقنية الايليزا .

النتائج: كان هناك اختلاف كبير في متوسط انترلوكين-6 عند المقارنة بين المرضى قبل وبعد غسيل الكلى (13.72+_0.74)مقابل (40.14 +_ 1.87)بيكوغرام/مل على التوالي ، $p0.0001 <$ ، ولكن لم يكمن هناك فرق كبير عند المقارنة بين المرضى قبل وبعد غسيل الكلى (13,72+_0.74) مقابل(40.14+_1.87) بيكوغرام/مل ومرضى ماقبل غسيل الكلى ($p 0.05 <$) . كان هناك اختلاف كبير في مستويات الانترلوكين-2 عند المقارنة بين المجموعة الضابطة ومجموعة المرضى ماقبل غسيل الكلى (2.08+_0.10)مقابل(3.18+-0.08) بيكوغرام/مل على التوالي $p 0.0001 <$. وكذلك كان هناك فرق كبير عند المقارنة بين مرضى غسيل الكلى قبل وبعد (3.71+-0.11) بيكوغرام /مل . كان هناك فرق كبير بيم مرضى غسيل الكلى في المجموعة الضابطة ومرضى مابعد الغسيل . كان هناك اختلاف كبير في مستويات انترلوكين -4 عند المقارنه بين المجموعة الضابطة وكل من مجموعتي المرضى قبل وبعد(1010.47+-22.16) ملغم / ديسليتر مقابل

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(1221.50+-21.98 و1673.04+-56.19 ملغم /ديسليتر) على التوالي ، p 0.0001 >) وكان هناك فرق كبير عند المقارنة بين مجموعات مرضى غسيل الكلى قبل وبعد.
الاستنتاج: كلاً من انترلوكين-2 و انترلوكين-6 مرتفعان بشكل ملحوظ عند مقارنة غسيل الكلى للمريض قبل وبعد . كان هناك زيادة كبيرة في مستوى انترلوكين -2 في المرضى بالمقارنة مع مجموعة السيطرة .

الكلمات المفتاحية : انترلوكين -2، انترلوكين-6، انترلوكين -4، الداء الكلوي بمراحله الاخيرة

Introduction

Chronic kidney disease (CKD) has acquired epidemic proportions worldwide due to an increase in the prevalence of its main causes; diabetes mellitus (DM), systemic arterial hypertension, obesity [1]. In accord with information from the National Health and Nutrition Examination Surveys (NHANES), the propagation of CKD (with the exception of end-stage CKD) in the USA was 13.1% for the (2011-2014) period [2] propagation of stages (3 to 5) CKD was about 5%, depend on data from the (NHANES) for the same duration in the USA and from Australia, India and China's data [2]. In addition, the number of patients with end-stage CKD (ESCKD) requiring intensive treatment has increased significantly in both developed and developing countries [3]. It has been frequently shown that progressed CKD is related with a case of chronic inflammation, as proved by either increased levels of several pro-inflammatory cytokines (IL-2, IL-6, INF-γ,IL-4, etc.) or changed levels of inflammation process and acute-phase proteins [4]. Furthermore individual genetic preparation [5]. The uremic state may raise the release of the peripheral cell of pro-inflammatory cytokines and delayed the removal of the latter leading to a net rise. More importantly, it has been appear that this chronic inflammation condition prognosticate all causes of cardiovascular death in HD patients [6]. Which suggests that the inflammatory perception of environmental inducement may determine the risk of death in this population. While, limited studies have estimated the inflammatory-profile of individuals in the earlier (CKD) stages [7] and [8]. IL-6 is a pro-inflammatory cytokine that is produced by several cells, including single cells and renal mesangial cells [9].

Material and Methods

Fifty patients with renal failure; Aged 18-80 years were enrolled in the study were collected from Al-Batool Teaching Hospital in Al-Kut, Wasit , Iraq from January to March 2018 were included in the study. The Scientific Committee of College of Medicine/Wasit University approved the study. For comparison, thirty normal persons were examined as a control for all parameters of the patients group. Interleukins IL-2 (RayBiotech, Inc./ USA), IL-4(Stem cell technology/ Kanada) and IL-6 (Anogen/Canada) were measured by using ELISA technique.

Results

There was a significant difference in the mean of IL-6 when compare between patients pre and post dialysis (13.72 ± 0.74 vs. 40.14 ± 1.87 pg/ml respectively, $p < 0.0001$), but there was no significant difference when compare between control (10.64 ± 0.78 pg/ml) and pre-dialysis patients ($p>0.05$), as shown in table (1).

Table (1): serum IL-6 in all study groups

Mean±SD	Control group	Patients	
		Pre-dialysis	Post-dialysis
IL-6 (pg/ml)	10.64 ± 0.78 b	13.73 ± 0.74 b	39.58 ± 1.83 a
LSD	3.865 **		
p-value	0.0001		

Means having with the different letters in same column differed significantly

There was a significant difference in IL-2 levels when compare between control and pre-dialysis patients group (2.08 ± 0.10 vs. 3.18 ± 0.08 pg/ml respectively, $p < 0.0001$), as well as, there was a significant difference when compare between pre and post dialysis patients (3.71 ± 0.11 pg/ml). There was a significant difference between control and post dialysis patients، as shown in table (2).

Table (2): serum IL-2 in all study groups

Mean±SD	Control group	Patients	
		Pre-dialysis	Post-dialysis
IL-2 (pg/ml)	2.083 ± 0.10 c	3.19 ± 0.08 b	3.71 ± 0.12 a
LSD	0.302 **		
p-value	0.0001		

There was a significant difference in IL-4 levels when compare between control and both pre and post patients groups (1010.47 ± 22.16 mg/dl vs. (1221.50 ± 21.98 & 1673.04 ± 56.19 mg/dl) respectively, $p < 0.0001$) and there was a significant difference when compare between pre and post dialysis patients groups, as shown in table (3).

Table (3): Serum IL-4 in all study groups

Mean±SD	Control group	Patients	
		Pre-dialysis	Post-dialysis
IL-4 **(pg/ml)**	1010.47 ± 22.17 c	1221.53 ± 22.43 b	1682.51 ± 56.52 a
LSD	118.90 **		
p-value	0.0001		

Discussion

The current study design to assess some interleukins and biomarkers in renal failure patients with renal dialysis. Fifty patients with age range (40-70 year). For comparison , thirty healthy subjects were enrolled in the study. All

parameters were measured for patients before and after dialysis .

There was a significant difference in the mean of IL-6 when compare between patients pre and post dialysis ($p < 0.0001$), but there was no significant difference when compare between control and pre-dialysis patients ($p>0.05$،(

Bruno Memoli and his colleges reported that hemodialysis associated induction of interleukin-6 formation by peripheral blood mononuclear cells. Interleukin-6 (IL-6) It has a complex set of biological activities, as example, growth and differentiation of B cells and manufacture of acute-phase proteins by the liver [10] appearing data showed that local stimulation of classical IL-6 and trans signaling pathway is implicated in kidney autoimmune and inflammatory disorder. Renal resident cells, consist of; endothelial cells, podocyte, tubular epithelial cells (TECs) and mesangial cells can execrate IL-6 under certain environment. Podocyte is the resident cell that expresses IL-6R, whereas others do not express IL-6R and not utilize classic IL-6 marking [9] . Other study indicate that IL-6 expression association with the starting and riskiness of acute kidney injury (AKI), but its assistance to pathogenesis stay unclear. This study established a important role for IL-6 in both the inflammatory process and the resolution of AKI. IL-6–deficient were resistant to HgCl2-stimulate AKI. The aggregation of per-tubular neutrophils was low in IL-6, and neutrophil depletion before HgCl2 administration significantly decreased AKI; these results explain the important role of IL-6 signaling in the determinate inflammatory procedure in AKI. Renal IL-6 expression and STAT3 activation in kidney tubular epithelial cells significantly elevated during the evolution of injury, indicate active IL-6 signaling. As well as a lack of kidney IL-6 receptors (IL-6R) prevents the activation of classical signaling pathways, IL-6 can enhance target cells together with a soluble form of the IL-6R (sIL-6R) in a method termed (trans-signaling). [11].

The probable causes of high levels of IL-6 in plasma of ESRD patients may be attached to (1) kidney dysfunction, (2) uraemia (and its sequelae , like; oxidative stress, fluid overload and susceptibility to infections) and (3) Kidney dialysis agents. also before the initiation of dialysis medication , patients with reduced kidney function already showing signs of inflammation have been associated with deterioration of kidney function with a significant rise in serum levels of cytokine [12]. Bolton et al. in a multiple retrogression analysis; Serum creatinine was the only determinant of IL-6 levels in a group of dialysis and pre-dialysis patients. One demonstration for these results may be the impaired kidney removal or IL-6 disruption [13]. Actually , ESRD patients have decreased urinary IL-6 receptor secretion than controls. IL-6 system and the Renal function remaining, appearing an relation between sIL-6R and the alternation rate of kidney function in the pre-dialysis phase, in addition to an combination between alterations in GFR and alterations in IL-6 through peritoneal dialysis (PD) therapy [14] .(

There was a significant difference in IL-2 levels when compare between control and patients groups ($p < 0.0001$), as well as, there was a significant difference when compare between pre and post dialysis patients groups. IL-2 is a large molecule with molecular weight 15-18 kD that produced by different types of immune cells such as T-lymphocytes, natural killer cells, and dendritic cells. Several studies recorded that IL-2

in renal failure patients are similar to control group [15] and [16]. This is due to the Vulnerability in activation and proliferation of T-cells to produced IL-2 in response to the increase in inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6. [17]. However, these suggestion are paradoxical with other studies which suggest that IL-2 levels increased in HD patients and that correlated with survival rate [18].Other study recorded that high concentrations in IL-2 in renal failure patients which underwent in transplantation operation [16]. Other studies have correlated high levels of IL-2 with improved survival for renal transplants [19]. Another study has linked high levels of IL-2 with renal rejections [20]. The increment in IL-2 concentration are usually correlated with several conditions as rheumatoid arthritis [21] scleroderma [22], gastric cancer [23] and lung cancer [24].

There was a significant difference in IL-4 levels when compare between control and patients groups ($p < 0.0001$) and there was a significant difference when compare between pre and post dialysis patients groups. It was found that serum level of IL-4 was considerably elevated following HD session in ESRD patients on chronic HD. The results were agreed with a study aimed at investigating the effect of HD on immune cells, particularly B lymphocytes, where IL-4, a cytokine produced by Th2 cells, was significantly increased in HD patients compared with renal dialysis [25]. These results may be attributed to urinary toxins that were expected to be higher in pre-dialysis patients and then reduced by HD. So, these results were not united in opinion with others study which suggest that serum concentration of anti inflammatory cytokines, consist of IL-4, were reduced following HD in CKD patients on chronic HD [26]. In this study, it was also detected that the difference in the mean serum level of IL-4 when compared between patients before HD session and healthy controls was statistically non-significant. Serum level of IL-4 was increase significantly in patients before HD compared with that of healthy controls. This result was agreed with a previous study [25].

On the other hand, the current study observed that there was a high significant difference in the mean serum level of IL-4 when compared between post-dialysis patients and healthy controls. It was demonstrated that IL-4 serum level was high in post-dialysis ESRD patients relative to that in healthy controls. This was approved by another study which performed that serum concentrations of Th2-related cytokines, consist of IL-4, were elevated significantly in HD patients contrast with controls [27].

Conclusions

There was a significant difference in the mean of IL-6 when compare between patients pre and post dialysis. There was a significant difference in IL-2 levels when compare between control and patients groups. There was a significant difference in IL-4 levels when compare between control and patients groups.

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