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SERUM LEVEL OF IL-6, IL-1β AND TNF-α IN PATIENTS OF CHRONIC RENAL FAILURE WITH MAINTENANCE HAEMODIALYSIS

[1]Mohemid M AL-Jebouri and [2]Huda R Al-Alwani

[1]Department of Microbiology. College of Medicine. University of Tikrit, Tikrit Iraq.

[2]Department of Microbiology. College of Medicine. University of Al- Anbar Iraq.

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***Correspondence for Author**
Prof. Dr. Mohemid M AL-Jebouri
[1]Department of Microbiology. College of Medicine. University of Tikrit, Tikrit Iraq.

ABSTRACT

Background: Chronic inflammation is a common feature of end stage renal disease which carries a heightened risk of atherosclerosis and other co-morbid conditions. Dialysis treatment per se can bring additional risk factors for inflammation such as increased risk of local graft and fistula infections, impure dialysate or bio-incompatible membranes. The present study was designed to determine the level of proinflammatory cytokines in chronic renal failure and whether a hemodialysis session leads to an acute substantial alteration in the plasma levels of the proinflammatory interleukins IL-6, IL-1β and tumor necrosis factor TNF-α. **Methods:** To determine the plasma level of IL-6, TNF-α, and IL-1β, 100 patients with ESRD were studied. The patients include 42% females and 58% males. Patients aged group between 18 to 80 years (mean=50.35±16.51). The control group aged (45.48±15.05). The blood samples (100 patients) were collected prior haemodialysis session and 50 control persons. The level of these cytokines in seum using ELISA method was estimated. **Results:** the level of these cytokines in serum of patients recently had dialysis treatment were high while the level of IL-6 was decreased progressively with dialytic age. The level of TNF-α and IL-1β also decreased with dialytic age but not as in IL-6. **Conclusion:** the results presented here indicated that prolonged treatment with dialysis can be considered a form of chronic stress that causes the progressive activation of monocytes which ultimately leads to monocyte exhaustion and dysfunction.

KEYWORDS: IL-6, IL-1β, TNF-α, chronic renal failure, haemodialysis.

1. INTRODUCTION

Cytokines are low molecular-weight regulatory proteins or glycoproteins secreted by white blood cells and various other cells in the body in response to a number of stimuli. These proteins assist in regulating the development of immune effector cells, and some cytokines possess direct effector function of their own. [1] Recent evidence indicated that chronic inflammation is a major contributor to morbidity and mortality in end stage renal disease (ESRD). [2] It has been proposed that a chronic inflammatory state could account for the high risk of ischemic heart disease in patients with ESRD. [3] Reduced renal function is a significant risk factor for cardiovascular events and death in chronic kidney disease (CKD) patients, and this risk is further increased when CKD has progressed to end-stage renal disease (ESRD) requiring dialysis initiation or kidney transplantation. Despite significant technical improvements in both haemodialysis (HD) and peritoneal dialysis (PD), the mortality rate in ESRD patients is still as high as 20% per year in patients undergoing renal replacement therapy. [4] The major causes of death in ESRD patients are cardiovascular disease (CVD) and infections, together accounting for up to 70% of all deaths in the patient populations studied. [5,6]

Patients with chronic renal failure commonly present with abnormalities of immune function strictly correlated with abnormalities of immune cell reactivity phenotype alternations of receptors and altered expression of cell surface receptors. These abnormalities are caused by impaired excretory function of kidneys and the accumulation of uraemic toxins in addition to bioincompatibility of dialyzer membranes. [7, 8]

The immune system of ESRD patients is impaired. In these patients, monocytes are preactivated and they overproduce cytokines such as TNF-α, IL-1, IL-6 and IL-10. [9] The contact of blood with dialyzer membrane leads to neutropenia and morphological changes of polymorphonuclear leukocytes. Experimental studies demonstrated stimulation and degranulation in these cells after their contact with dialyzer membranes. These abnormalities may likely be associated with the process of “inefficient phagocytosis” elicited by the adherence of polymorphonuclear leukocyte to foreign surface. Furthermore, inflammatory mediators are released in the course of degranulation. Another process engaged in blood and dialyzer membrane interactions is the activation of monocytes leading to the increased release of IL-1, which in turn leads to the release of IL-2 by monocytes. [10, 11] Numerous research studies on the synthesis and the release of proinflammatory cytokines IL-1β, IL-2, IL-6, IL-8

and TNF-α in patients with chronic renal failure on maintenance haemodialysis provide contradictory data. Although some of these studies demonstrated increased serum levels of the proinflammatory cytokines prior to and in the course of haemodialysis, other studies indicated that cellular activation and cytokine synthesis is only transient and the increase of the serum levels is rather moderate. [12,13,14] Stimulation of peripheral blood mononuclear cells (PBMC) can lead to the synthesis and release of proinflammatory cytokines. Several studies have shown that plasma levels of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-a (TNF-a), as well as specific cytokine inhibitors such as interleukin-1 receptor antagonist (IL-1Ra), are elevated among patients who are on HD. These cytokines have been incriminated in the short- and long-term morbidity experienced by HD patients. [15] Bologa and colleagues. [16] Found a significant correlation between plasma TNF-a and IL-6 and the degree of hypoalbuminemia and dyslipoproteinemia among HD patients. This study also found that plasma IL-6 levels were predictor of mortality among these patients. Likewise, Kimmel and colleagues. [17] found that elevated plasma levels of IL-1, TNF-a, IL-6, and IL-13 among HD patients were significantly associated with an increased relative risk of death. Monocyte belong to the main effector cells of the immune system responsible for the first-step control of bacterial, viral, or fungal infections. Apoptosis of monocyte may occur constitutively during aging or may be induced or reverted by inflammatory mediators and cytokines. [18] It remains unclear whether a relationship exists between the cytokines release pattern *vs* dialytic age. The present study was designed to investigate the serum levels of IL-1β, TNF-α and IL-6 of patients with CRF treated with conservative therapy, and of patients in dialytic therapy are assessed versus dialytic age.

2. MATERIALS AND METHODS

2.1. Patient: this study involved a total of 150 individuals in three groups, whose mean age, sex and clinical data are listed in Table 1. There were 20 patients with CRF who were recently began the dialysis treatment (≤1 weak), (80) haemodialysed patients (HD) , and 50 individuals as control group (CON). On the basis of the dialytic age, the HD patients were divided into four subgroups: Short-term HD patients (age of dialysis ≤ 1 month, 10 patients), medium-term HD patients (age of dialysis ≤ 6 month, 23 patients), long-term HD patients (7 months-1year, 18 patients) and very long –term HD patients (≥1 years, 29 patients). Dialysis treatment comprised 2-3 hour sessions a week using dialysis solution formed from acidic bicarbonate and basic bicarbonate.

2.2. METHOD

Blood samples (3-4 ml) of blood were taken from both patients and control groups. The bloods of HD patients were collected before the dialysis session. The blood samples were collected in white tube, after the clotting of blood the centrifugation was performed. The sera collected were frozen at – 20 ^{o}C prior to analysis. IL-1β, IL-6 and TNF-α were determined in samples with a commercial enzyme-linked immune-sorbent assay kit (abcam, USA) in accordance with the manufacturer's instructions. The lower limit of detection was 0.95 pg/ml for IL-1β, 8pg/ml for TNF-α and 3pg/ml for IL-6.

2.3. Statistical analysis

Statistical analysis was performed with the SPSS software ver. 19 , Bar chart , t- test for independent sample and ANOVA analysis with LSD to compare more than two groups were used.

3. RESULTS

Serum levels of IL-1β, TNF- α, IL-6 of controls, patients with CRF and from short-, medium-long- and very long-term HD patients are shown in Figure 1(A, B). The Figure 1A shows the difference of cytokines concentration in patients and control group, while the Figure 1B shows the concentration of three cytokines in patients according to the dialytic age. The level of IL-6 in patients of CRF (recently started the dialysis, 1-2 session of dialytic treatment) with period of dialysis ≤ 1 week is high (230.9 pg/ml) which had a significance difference *p* value <0.05 from group of short-term dialysis (≤ 1 month) who had concentration (124.1 pg/ml). There was a significance difference between group one (≤ 1 week) and all groups including controls. There was a significance difference between group two (≤ 1 month) with other groups including control. There was no significance difference *p* value > 0.05 between other three groups (medium-, long- and very long- term of dialysis treatment) . The level of IL-1 in group of ≤ 1 week was high compared to other groups, while there was no significance difference between other groups (P ≥ 0, o5). The level of TNF-α in serum of group ≤ 1 week and group ≤1 month was high compared to other groups(P < 0.01) and the group of 1-6 month revealed a significance difference compared to other groups tested (P < 0.05). There was no significance difference P ≥ 0.05) between sex and concentration of each three cytokines as shown in Table 2. The statistical analyses of the data presented in this study did not reveal a relation between each one of cytokines(IL-6,IL-1,TNF) and the type of disease as shown in Tables (3,4,5) respectively.

Table 1: The relation between the sex, age and clinical data of patients studied.

Patients	Sex	Age	hypertension	diabetic	stone	Unknown causes	Renal transplant	Renal rejection
100	Male(57) Female(42)	50.35±16.51	54	27	25	26	9	4

Table 2: The relation between sex and the concentration of three cytokines tested.

	sex	Mean(SD)	T test	P value
il_6	Male n=58	71.80±108.5	-1.053	0.295
	Female n=42	96.0±1192		
il_1	Male	27.1379±21.9526	-0.92	0.36
	female	31.4286±24.4165		
TNF-α	Male	82.6207±72.3191	-0.70	0.42
	female	93.4286±80.9280		

Table 3. The relation between type of diseases and concentration of IL-6.

Hypertension.		N	Mean	Std. Deviation	t test	p value
IL-1	**yes**	56	29.14	24.32	0.09	0.92
	no	44	28.68	21.47		
diabetes						
IL-1	**yes**	27	25.63	20.33	-0.87	0.38
	no	73	30.16	23.92		
stone						
IL-1 **yes**		25	26.36	20.33	-0.87	0.38
no		75	29.80	23.92		
Unknown causes						
IL-1 **yes**		26	32.5	26.17	0.91	0.36
no		74	27.69	21.83		

Table 4: The relation between IL-1 and the type of diseases.

	diabetes		N	Mean	Std. Deviation	t test	p value
il_6		**yes**	**27**	**84.52**	**98.98**	**0.13**	**0.89**
		no	**73**	**81.02**	**119.01**		
	hypertension						
il_6		**yes**	**56**	**94.34**	**128.09**	**1.23**	**0.22**
		no	**44**	**66.22**	**90.60**		
	Unknown causes						
il_6		**yes**	**26**	**75.50**	**99.93**	**-0.33**	**0.73**
		no	**74**	**84.24**	**118.42**		
stone							
il-6		**yes**		**93.98**	**117.49**	**0.60**	**0.54**
		no		**77.96**	**112.63**		

Table 5: The relation between TNF-α and the type of diseases.

hypertension		N	mean	Standard error	t-test	P value
TNF-α	yes	56	86.43	66.94	-0.10	0.92
	no	44	88.09	86.67		
diabetes						
TNF-α	yes	56	86.43	66.94	-0.10	0.92
	no	44	88.09	86.67		
unknown						
TNF-α	yes	26	100.27	110.56	1.02	0.30
	no	74	82.55	59.43		
stone						
TNF-α	yes	25	78.88	42.10	-0.62	0.53
	no	75	89.92	84.20		

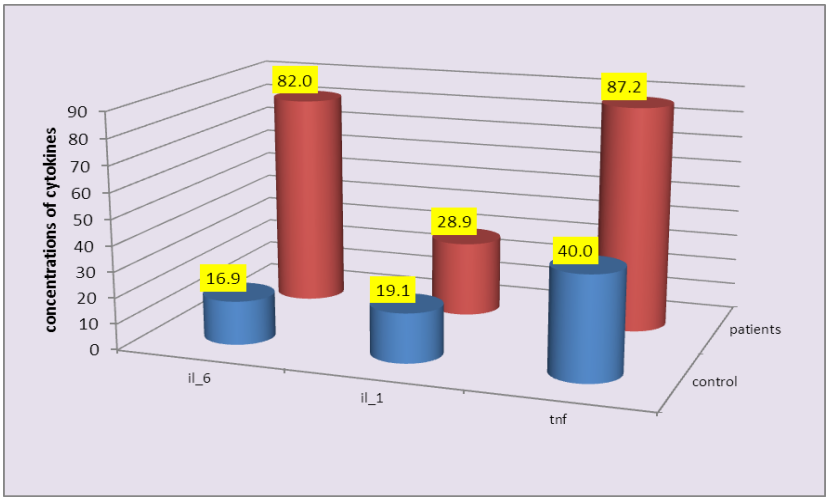

Figure 1, A . The concentration of IL-6, TNF and IL-1β in patients and control group.

Figure 1B: The concentration of three cytokines in patients according to the age of dialysis.

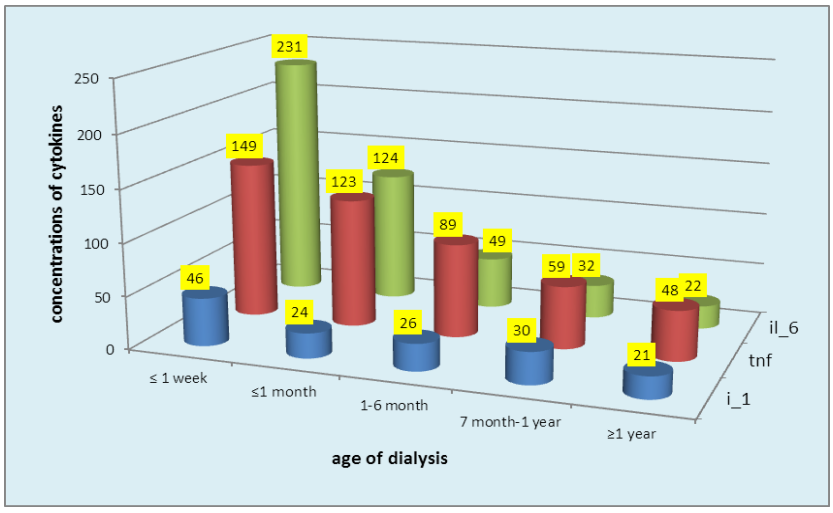

Figure (2B). The figure show the concentration of three cytokines in patients (Y axis) according to the age of dialysis (X axis)

4. DISCUSSION

ESRD gives rise to various cytokine disturbances and to a state of hypercytokinemia involving anti-inflammatory cytokines such as IL-10 as well as pro-inflammatory cytokines such as TNF-α and IL-6. Deterioration of kidney function leading to reduced removal rate as well as increased cytokine generation are thought to be the major culprits for the increased levels of circulating cytokines in ESRD. [19,20,21] Numerous research studies on the synthesis and the release of proinflammatory cytokines IL-1β, IL-2, IL-6, IL-8 and TNF-α in patients with chronic renal failure on maintenance haemodialysis provide contradictory data. Although some of these studies demonstrated increased serum levels of the proinflammatory cytokines prior to and in the course of haemodialysis, Other studies indicated that cellular activation and cytokine synthesis is only transient and the increase of the serum levels is rather moderate. [10,11,12]

The results presented here were almost similar to the findings of Mohsen, et al. [22] which showed an elevation of TNF-α in patients who were not yet been dialyzed and decreased in HD patients, Furthermore, the presented results were different from those of Alvin et al which showed that no difference in plasma IL-1β or TNFα concentrations in healthy control, dialysis patients, and chronic renal failure patients. and also confirm with Roberto ,et al. [23] ,but not confirmed with Andre Herbelin et al. [24] report which improved that no significance difference between first dialysis patients and long term –dialysis patients because in both groups the IL-6 values were high. Although activated monocytes and T cells could both be responsible for increased circulating TNF-α and IL-6 levels in these patients, one must also consider the possibility that chronic renal failure itself could participate in dysregulation of the production and elimination of these cytokines. Indeed, the reduced glomerular filtration rate could lead to their defective clearance from the plasma.

The present results showed that IL-6 and TNF-α levels were 230.9 and 149.1 respectively which showed an increase more than IL-1β. [45, 65] in patients recently or first dialysis session if compared with dialysed patients and control, This might be due to impaired excretory function of kidneys and the accumulation of uremic toxins. The possibility that IL-6 and TNF-α but not IL-1β are generated in these patients could not be excluded. Alternatively, it could be due to the fact that IL-1β can remain cell-associated after its induction. [25] whereas IL-6 and TNF-α are immediately secreted. [25, 26] It can thus be proposed that the increased plasma levels of IL-6 and TNFs in not yet dialyzed patients are associated to an activation

state of monocyte [in elevated circulating level IL-6]. Also our results confirm with Yannick Le Meur et al. [27] who noted that monocytes from HD patients in whole blood culture are hyporesponsive to phytoheamagglutinin(PHA) and lipopolysaccharide (LPS) for their IL-1, TNF-α, IL-6 production. Monocytes and monocyte-derived dendritic cells have been shown to display decreased endocytosis and impaired maturation when cultured in uremic serum.[28] or when obtained from ESRD patients. [29] In addition to nondialysis related factors, it seems reasonable to suggest that the dialysis procedure per se represents additional stimulation of the inflammatory response.

Therefore, our results presented here showed high value of IL-6 and TNF-α in short – and medium-term haemodialysis patients. Activation of the proinflammatory system in HD patients may be due to three mechanisms: Susceptibility to local graft and fistula infections, inflammatory response induced by bioincompatible dialysis membranes and exposure to contaminated dialysate containing cytokine-inducing substances such as endotoxins. [30,31] microbial contamination of dialysis fluids which represent the main stimulants to production of inflammatory mediators in dialysis. However, Takahashi et al. [32] demonstrated that both haemodialysis and peritoneal dialysis generate an increase in blood mononuclear cell IL-6 mRNA expression and plasma IL-6 levels. Caglar et al. [33] showed that circulating IL-6 levels increased following haemodialysis providing evidence of haemodialysis-induced delayed inflammatory response. Several factors related to haemodialysis have been proposed to contribute to the generation of IL-6 and/or enhance the inflammatory effect of IL-6, specifically use of bioincompatible membranes and nonsterile dialysate. Finally, as many cytokine encoding genes are also expressed in adipocytes it has been estimated that the adipose tissue may account for as much as 20% of systemic IL-6 concentrations. [34] Thus, visceral adiposity may be yet another reason for elevated IL-6 levels in ESRD patients. [35] Also clinical study in ESRD patients have shown that serum creatinine is a major determinant of plasma IL-6 levels. [36]

The results presented here were almost similar to those obtained by Mohsen, et al which prove that concentration of TNF- decrease in HD patients and explain this dropping that haemodialysis process has a beneficial effect on ESRD patients by reducing or stopping TNF- release from monocytes by removal of uremic toxin. This explanation was not supported by present findings because the patients had a high concentration of urea and creatinine were 213.9±38.16 and 5.35±0.95 respectively. These present results were different

from those of Andre Herbelin, et al. [24] who showed that there was no difference between long-term and not yet dialyzed patients. Also there is other explanations for dropping of TNF-α in HD patients ,in addition to exhausation of monocytes, TNF-α may be increase because presence of TNF-α binding protein as well as the use of heparin during the haemodialysis procedures which are known to bind TNF-α and block its action. [37] The data presentd here showed that IL-6 concentration decreases with increase the dailytic age which almost similar to results obtained by Grazia et al. [38] and Balakrishan et al [39]. This might be due to that the capacity of purified monocytes from long-term HD patients to release cytokines is impaired because of the chronic exposure to exogenous stimuli leading to chronic in vivo stimulation. [40, 41] Moreover, the expression of CD14 on peripheral blood monocytes has been demonstrated to be significantly lower in HD patients compared to undialyzed uraemic patients and healthy controls. [42] Furthermore, the monocytes from chronic dialysis patients developed characteristics of apoptosis to a significantly higher degree compared to healthy control subjects. The enhanced rate of apoptosis of monocytes from dialysis subjects may be related to chronic uraemia and most probably reflects an intrinsic cellular defect leading to endogenous endonuclease activation. [43]

5. CONCLUSION

These results showed that the decreased value of cytokines in patients of dialysis with increase the age of dialysis depressed monocytes functions found in patients on chronic dialysis may be attributed to a chronic recurrent activation and consequent exhaustion of the cell. [44]

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