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CYTOKINES REGRESSION ACCORDING TO AGE OF HAEMODIALYSIS OF IRAQI PATIENTS DURING MAINTENANCE

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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 might associated with flacuation in levels of interleukins of serum patients. The present study was designed to determine the level of proinflammatory cytokines in chronic renal failure and whether a haemodialysis 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 with reference to age. **Methods:** To determine the plasma level of IL-6, TNF-α, and IL-1β, 100 patients with ESRD were studied as described elsewhere.[1] Patients aged between 18 to 80 years. **Results:** Using the linear regression analysis, it was found that the IL-6 level was decreased with increase the dialysis age (P value < 0.05), and the regression pattern of IL-6 with dialysis age was differ from TNF-α and IL-1β.This was observed in the different values of coefficient determination (R^2) factors. **Conclusions:** IL-6 revealed the highest value R^2= (0.418) followed by TNF-α which showed R^2 value (0.225), while IL-1β with R^2 factor = 0.099.

KEYWORDS: Heamodialysis age, Cytokines regression, Iraqi patients.

1. INTRODUCTION

The three cytokines, interleukin-1 (IL-1), interleukin- 6 (IL-6) and tumor necrosis factor-α (TNF-α) are of particular significance. Although they are different proteins transcribed from different genes, they share remarkable similarities in their biological properties. They all induce fever, hypotension, and inflammation when injected into the animals or human

subjects.[2,3] It should be noted that a change in concentration does not necessarily mean a rise in concentration. As most cytokine concentrations are increased, this may be due to that reduced renal clearance plays an important role in their retention.[1] A possible role of increased TNF-α levels in the development of renal impairment before dialysis should be considered. In fact, some authors have shown that TNF-α infused in rats can induce metabolic acidosis and acute renal failure.[4] Moreover, the presence of a neutrophil stimulatory reduced oxygen species (ROS) factor in serum from nondialyzed UR patients and suggested that it is specifically associated with renal dysfunction. Although this serum factor was found in the range of 1,000 dalton molecular mass.The role of TNF-α, known to induce ROS production by phagocytic cells, remains to be investigated in nondialyzed UR patients. Progressive renal damage may indeed result from TNF-α induced production of ROS by neutrophils in the vascular membrane of the kidney.[5] Control of IL-1 is affected not only by different cytokines but also by many other variables that produce a modulating effect.[6] Some of these factors affecting LPS monocyte activity are :(i) LPS heterogeneisty, as variations in the hydrophobic region of lipid A between bacterial strains, due to the number, type and location of fatty acids are critical for cell activation; note that some glucosamine precursors and analogues of lipid A act as LPS antagonist blocking its bioactivity.[7] (ii) Endotoxin concentration, as low amounts act through the 55 kDa mCD14 receptor, while high levels directly activate endothelial and epithelial cells by the 53 kDa sCD14 soluble receptor and macrophages by a 73 kDa LPS-binding protein(LPB) acting as a functional receptor.[8] (iii) LPS detoxification, as the deacylation induced by an acyloxyacyl hydrolase from granulocytes creates an LPS antagonist molecule.(iv). LPS complexing with host proteins that could enhance LBP or inhibit cell activation.[9.10]

2. MATERIALS AND METHODS

blood samples (3-4 ml) of blood were taken from both patients and control groups. The blood 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.[1]

STATISTISTIAL ANALYSES

The linear regression analysis was utilized.

3. RESULTS

Cytokines level in the patients were higher than in control group as in Table 1.

Table 1 Differences between patients and control in cytokines levels.

Cytokine type Pg/ml	Patients* NO:100	Control NO: 50
IL-1β	28±23.00	19.10± 5.32
IL-6	81.97±133.48	16.90± 5.82
TNF-α	87.16±75.84	40± 11.74

*All comparisons were significant, for all ***P value <0.003***

Relation of Cytokines Level with Dialysis Age

The concentration of IL-6, TNF-α were decreased with increase the dialysis age, IL-1β also decreased but not as in other two cytokines. There was a significant difference between concentrations of three cytokines ***(P value*** < 0.05) as shown in Figure 1.

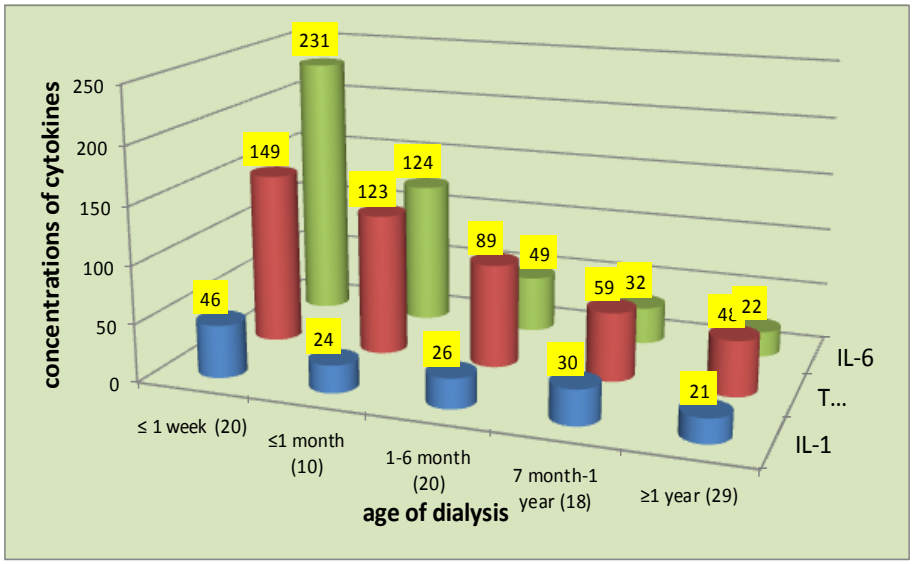

Figure 1. The relation of cytokines concentrations with dialysis age, ( ), denote the number of patients.

Comparison between Regression of three Cytokines with Dialysis Age.

By using the linear regression analysis, it was found that the IL-6 level was decreased with increase the dialysis age(P value < 0.05) and the regression pattern of IL-6 with dialysis age was differ from of TNF-α and IL-1β. This was observed in the different values of coefficient

of determination (R^2) factors. IL-6 had the highest value R^2= (0.418) followed by TNF-α which showed R^2 value (0.225), while IL-1β with R^2 factor = 0.099. TNF-α level also decreased significantly with dialysis age(P value < 0.05), IL-1β also was decreased according to dialysis age, but this relation was not significant (P value > 0.05). These results showed in Figures 2-4.

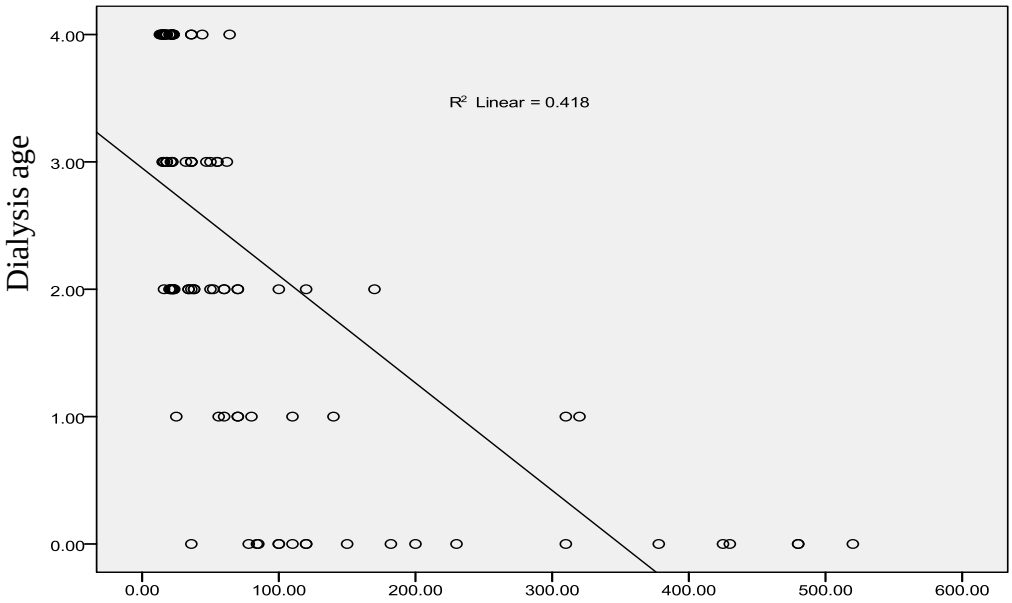

Figure 2. Linear regression pattern of IL-6 with dialysis age.

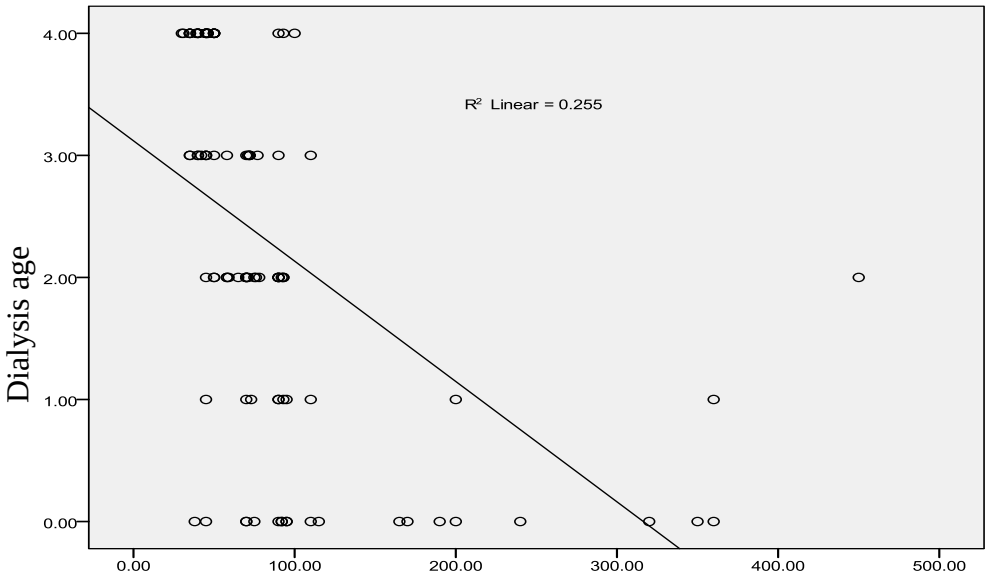

Figure 3. Linear regression pattern of TNF-α with dialysis age.

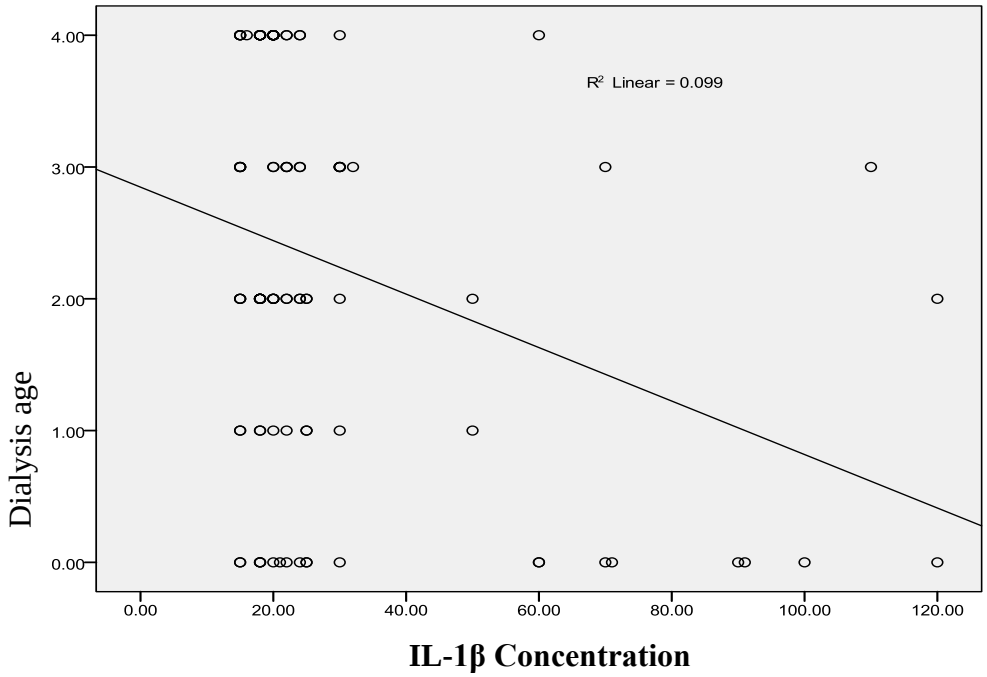

Figure 4. Linear regression pattern of IL-1β with dialysis age

4. DISCUSSION

High level of cytokines in the patients of this study might be decreased in accordance with dialytic age especially for IL-6 and TNF-α and the declining in patients cytokines level did not reach to level of control even in very long period time of dialyzed patients. The declining in the level of cytokines with increase the dialysis age was significant. This result was consistent with Malaponte *et al.*[11] The reduced level of cytokines was attributed to monocytes cell exhaustion that causes by chronic activation of these cells by HD related factors. The regression of IL-6 with dialysis age was more than TNF-α. This due to that the initial concentration of IL-6 was more than TNF-α, therefore the decline of IL-6 was more rapid than TNF-α.

High level of these cytokines do not indicate a good immunity, but result in immune failure, because this response occur in the absence of specific pathogen, this response result high level of IL-6, IL-6 are followed by secretion of IL-10 in attempt to limit the inflammatory response.[1,12] The elevation in cytokine level in present patients was mostly due to renal failure *per se* that lead to retention of these cytokines in their blood, in addition to continuous activation of monocytes cells by HD related factors. There is an intermittent multiple stimulation during each HD session. Among these components are acetate, pyrogenic substances, and activation of the complement mainly as a result of dialysis membranes. This

continuous activation mostly lead to monocytes exhaustion, that cause defect in immune system of these patients.

5. CONCLUSION

The haemodialysis process in this centre was not adequately efficient. This was indicated by high serum level of urea and creatinine in addition to high level of cytokines in the majority of patients particularly with age. Among these components are acetate, pyrogenic substances, and activation of the complement mainly as a result of dialysis membranes. This continuous activation mostly lead to monocytes exhaustion, that cause defect in immune system of these patients.

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