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Original Research Article

Correlation between Plasma Interleukin-18 Level and Disease Activity in Jordanian Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Interleukin 18 (IL-18) is a newly defined cytokine that has an important role in the Th1 type immune response and it shares similar functional properties with IL-12. Elevation of IL-18 levels in autoimmune diseases such as SLE has been reported in previous studies whereas in Rheumatoid Arthritis (RA) no study has been conducted in plasma IL-18 on the same aspect.
Aims & Objectives: To study the IL-18 levels in the plasma of Jordanian patients suffering from Rheumatoid arthritis and to correlate the disease activity and IL-18 level.
Materials and Method: The study includes forty-one RA patients in experimental group, and forty-one as a control group, sex and age matched apparently healthy subjects. Plasma IL-18 levels were determined using enzyme-linked immuno sorbent assay (ELISA).
Results: IL-18 levels were significantly elevated in the RA patients compared to the controls ($p< 0.0001$). However, there was no significant correlation with disease activity in RA patients ($r= -0.205$, $p=0.198$, $r= -0.196$, $p=0.22$.respectively).
Conclusion: Elevated IL-18 levels were noticed in patients with RA. IL-18 levels are not correlated with disease activity in RA patients.
Keywords: Plasma Interleukin-18 Level, Disease Activity, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease associated with destruction of cartilage and underlying bone in the joint. It is a common autoimmune disease of joints. RA is thought to be a Th1 associated disease (Dayer, 1999). [1]

Interluekin (IL)-18, formerly called IFN-γ-inducing factor, is a novel Th1 cytokine produced by kupffer cells, activated macrophages, keratinocytes, intestinal epithelial cells, osteoblasts and adrenal cortex cells (McInnes, et al.,[2] and Dinarello[3]). It plays an important role in the Th1 response to toxic shock and shares functional similarities with IL-12 (Dinarello[4]). IL-12 can induce the production of IL-18 and has a synergistic effect with IL-18 on the activation of natural killer (NK) and cytotoxic T lymphocytes (CTL) (Fehniger, et al., 1999). [5]

The association of IL-18 with pathological condition had been evaluated in

many diseases including the hemophagocytic lympho histiocytosis (Takada, et al., 1999), [6] Crohn's disease (Monteleone, et al., 1999) [7] and leukemia (Taniguchi, et al., 1997). [8] Connective tissue diseases are important causes of morbidity and mortality. They are autoimmune in nature with variable manifestations of both clinical course and management strategies. Factors that govern severity, response to treatment and outcome are largely unknown. Genetic factors, cytokines and environmental factors have been indicated in the pathogenesis and pathology of these diseases.

Aims & objectives

This study aims at measuring levels of Interleukin-18 (IL-18) in plasma samples taken from Jordanian patients suffering from Rheumatoid Arthritis (RA) and to correlate plasma IL-18 levels with disease activity.

MATERIALS AND METHODS

Sample selection

This research was conducted on blood samples obtained from patients referred to the rheumatology outpatient clinic of the Jordan University Hospital. The blood samples were collected from 41 patients including 28 females and 13 males with an age range between 22 and 70 years, all had confirmed diagnosis of RA, according to the 1987 revised American Rheumatism Association criteria for the classification of RA (Arnett, et al., 1988) [9] apparently healthy individuals with 41 age and sex matched, were included as a control.

Data collection methods:

1. ***Blood specimen collection***
   Seven ml of peripheral blood was collected from each patient and control individual into EDTA containing tube using Vacutainer system (Becton Dickinson Vacutainer System, France). Plasma was separated within 4 hours by centrifugation at 2000g at 4°C for 10 minutes, then it was aliqouted and stored at -70°C until it was analyzed (Wong, et al., 2000). [10]
2. ***Evaluation of disease activity***
   The disease activity of RA patients was evaluated in line with the clinical examination depending on the number of swollen joints and their tenderness. The disease was considered active when one or more of these clinical manifestations were present, and inactive in the absence of these clinical manifestations.
3. ***IL-18 Determination assay***
   Plasma IL-18 concentrations of patients and control subjects were measured by Enzyme Linked-Immuno-Sorbent Assay (ELISA) using human IL-18 ELISA Kit manufactured by Medical and Biological Laboratories.

Data analysis and interpretation

Quantitative continuous measurements were expressed as mean, median, standard deviation (SD) and range. Two-tailed T-test was used for comparison between two independent sample populations at 95% confidence level ($P<0.05$).Pearson correlation to assess the correlation between IL-18 concentrations and swollen and tender joint count in Rheumatoid Arthritis patients. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistical software for windows, Version 9.0 (SPSS, Chicago, IL, USA). A probability (P) value of <0.05 was considered as indicating a significant difference.

RESULTS

RA patients and their control group

Forty-one Jordanian patients with RA consists of 28 females and 13 males, (mean age ± SD = 46.4 ± 14.7 yr), were recruited for this study. The mean duration

of the disease at the time of patient's evaluation was 10.2 ± 8.9 yr, ranging from 1-32 yr. Forty-one, sex-and-age-matched, apparently healthy, 28 females and 13 males, (mean age ± SD = 39.2 ± 8.1 yr), ranging from 23 to 57 yr were recruited as control subjects.

IL-18 levels in the plasma of RA patients and their control group

The mean concentration of IL-18 in RA patients was 519 ± 268 pg/ml ranging from 67 to 1156 pg/ml. The levels in the plasma of control group were ranging from 68 to 420 pg/ml with a mean value of 287±77. The comparison of both patients versus controls IL-18 levels was statistically significant, ($p<0.0001$). When the levels of IL-18 were studied according to the disease activity, there were significant differences between the levels of IL-18 as shown in table 1.

Table (1): Plasma Levels of IL-18 of RA and the control group (values in pg/ml).

1L-18 Pg/ml	RA Patients N=41 (a)	Active RA N=22 (b)	Inactive RA N=19 (c)	Control Group N=41 (d)	Statistical comparisons (P value)
Mean+ .SD Median Range	519+_ 268 402 (67-1156)	480+_256 388 (225-1156)	564+_ 281 619 (67-1087)	287+_77 305 (68-420)	(a)/(d)*p.< 0.0001 (b)/(d)*p.< 0.0001 (c)/(d)*p.< 0.0001 (b)/(c) p.= 0.324
*p(significant)					

When we studied the correlation between IL-18 level and the swollen and tender joint count, we were unable to demonstrate any statistical significance with a correlation factor of ($r = - 0.205$, $p = 0.198$) and ($r = - 0.196$, $p = 0.220$) as shown in Fig 1 - a and b respectively.

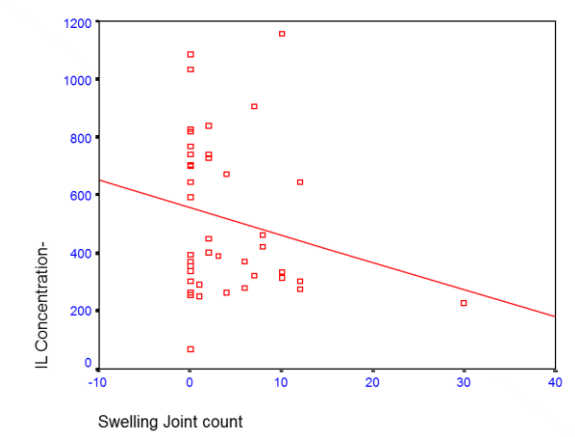

Figure (1a): correlation between IL-18 level and swollen joint count in RA patients.

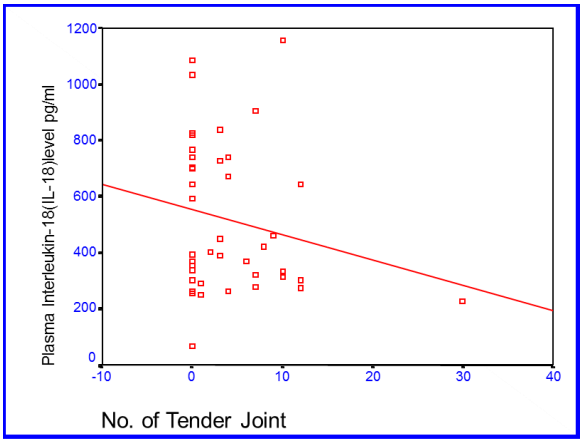

Figure (1 b): correlation between IL-18 level and Tender joint count in RA patients.

DISCUSSION

The findings for RA showed that the plasma IL-18 levels were significantly elevated in patient with RA as a group, and in patients with active and inactive disease as subgroup, in comparison to the control group the mean concentration 402, 388, 619 and 305 Pg/ml respectively table (1). However, there was no significant statistical difference between the patients with active and inactive.

Similar to this study findings, Bresnihan [11] reported that the serum levels of IL- 18 was significantly higher in RA in comparison to psoriatic arthritis ($p <0. 001$), psoriatic arthritis, and also they found no

statistical significant correlations between serum levels of IL- 18 and the number of swollen joints, which confirms our results (Bresnihan, et al. 2002). [11] Gracie et al [12] also showed an elevation of IL- 18 in 67% of synovial fluids obtained from patients with RA. Munakata et al. [13] also found IL-18 significantly elevated levels in both serum and synovial fluid obtained from patients with RA in comparison to those obtained from patients with osteoarthritis (OA) patients and normal volunteers. Yamamura [14] and his co- workers also reported similar results.

CONCLUSION

Elevated IL-18 levels were noticed in patients with RA.Although elevated IL-18 levels were observed in patients with RA, there was no statistical difference of the level in the active and inactive groups.

Recommendation

We recommended to evaluate other types of autoimmune diseases such as Systemic lupus erythematosus (SLE) and Behcet's disease, and correlate plasma interleukin 18 levels with disease activity. Further study can be conducted using large sample.

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