Original Article

Possible Role of Interleukin-6 in Rheumatoid Arthritis

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Summary:

Background: *Rheumatoid Arthritis (RA) is an autoimmune disease. Many etiological agents are proposed to play a role in its pathogenecity. One of these factors is cytokines such as Interleukin6.*
Material & Methods: *ELISA method has been used for IL-6 estimation in 75 RA patients in comparison with 61 SLE as patient controls and 39 apparently healthy controls.*
Results: *This study showed that there was an elevation of IL-6 in the sera of RA patients with high significant differences between RA patients and controls (P< 0.001). Moreover a good correlation between IL-6 level & RF titer were observed. However, for most patients with high IL-6 were shown to be HLA-DR4.*
Conclusions: *Interleukin-6 play a crucial role in the disease which may be participate in the severity of RA & subsequently its treatment.*

Key words: *RA, IL-6, RF, HLA-DR4, ELISA, Microlymphocytotoxicity*

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Introduction:

The best knowledge of RA treatment depends on the studying the cellular & humoral factors that involved in the disease pathogenecity. On the tope of these factors are the cytokines, including IL-6 as an inflammatory factor. Recent study showed that there is a cross talk between IL-1 and IL-6 signaling pathways in RA synovial fibroblasts [1]. While a number of interleukins such as Interleukin-1 (IL-1) and (IL-10) seem to be pleiotrophic in their effects, (IL-6) may be considered the prototrophic cytokine. This is reflected in the variety of names originally assigned to 11-6 based on function, including Interferon (32, IL-1 inducible 26kD Protein, Hepatocyte Stimulating Factor, Cytotoxic Tcell Differentiation Factor, B cell Differentiation Factor (BCDF) and

/ or B cell Stimulating Factor 2 (BCSF2). All these activities associated with inflammatory process [2]. So IL-6 is considered as a pleiotrophic inflammatory cytokine produced by T cells, Monocytes, macrophages and synovial fibroblasts [3]. Originally identified as a factor that induces the final maturation of B cells into plasma cells. Recently an interesting studies involving the IL-1 and IL-6 in initiating the significant pathway in RA symptoms. Interleukin-6 was observed to be involved in diverse biologic processes, such as the activation of T cells, induction of the acute-phase response, stimulation of the growth and differentiation of hematopoietic precursor cells, and proliferation of synovial fibroblasts results in synovial inflammation and ultimately joints damage [4].. The current study is a trail to estimate IL-6 concentration in the patients' sera in comparison with patient controls and apparent healthy controls. This , however, might open a gate for entrance into the treatment of this disease.

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Subjects & Methods:

Seventy-five Rheumatoid Arthritis (RA) patients' sera samples have been studied for IL-6 in comparison with 61 SLE patients as patient controls besides 39 apparent healthy individuals. IL-6 has been estimated by using ELISA technique [Diaclone, France Lot. No. 1006-24]. All patients were diagnosed according to the modified criteria [revised criteria of the American Rheumatism Association [5].. In this study HLA-typing using micro-lymphocytotoxicity by were assessed [6].

Statistical Analysis:

All the data have been analyzed statistically using Kriiskal- allis test and Mann-Whitney analysis for measuring the differences between the studying groups [7]..

Results::

I. Interleukin-6 Level in the sera of RA patients and control groups:

The results of IL-6 estimation in the sera of RA patients, patient controls and apparent healthy individuals are listed in the table-l. This table shows that there is high significant differences between IL-6 levels in the patients sera and controls (P < 0.001 for each comparison), with a median of 195, 50, and 8 pg / ml for RA patients, patient controls and healthy controls respectively.

Table -1 IL-6 concentrations in the RA atients sera and control rou s

Interleukin-6 (IL-6) concentration in pg / ml	Sporadic RA (75) *	Patient Control [PC] (61)	Healthy Control [HC] (39)
Range	21-576 pg. / ml	28-570 pg. / ml	1-157 pg. / ml
Mean ± SD	216.2 ± 159.3	137.7 ± 166.58	16 ± 2 6.54
Median	195	50	8
P (Kruskal-Wallis) for the three groups differences = <0.001 P (Mann-Whitney) for the differences between two groups RA vs. PC = < 0.001, RA vs. HC = < 0.001			

***** = *No. Between brackets represents the No. of patients.*

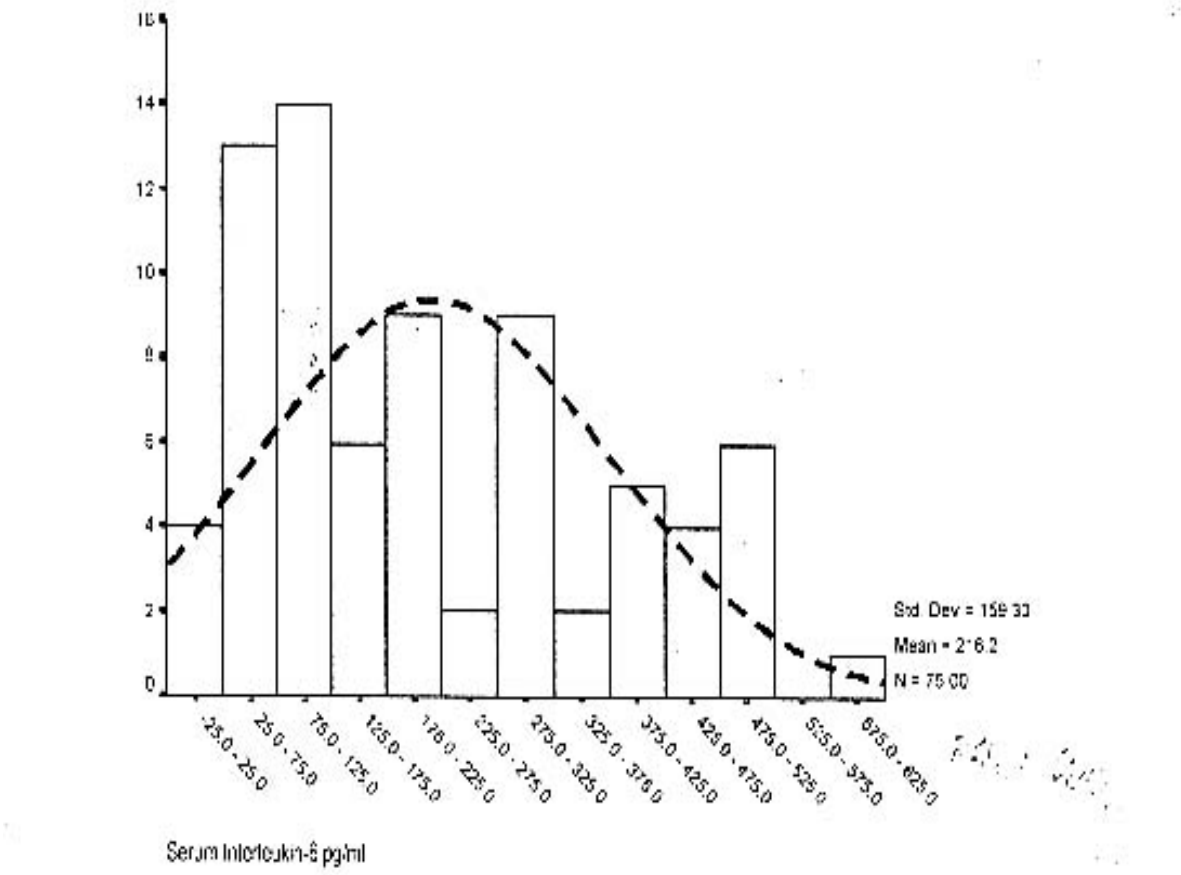

Figure 2. Distribution frequencies of IL-6 concentrations among RA patients sera.

The above figure reveals the distribution of IL-6 concentration in RA patient's sera according to its frequencies. This figure reveals that there was a normal distribution for the frequencies of IL-6 concentrations among RA patients sera, though the highest frequencies are observed between 25-125 pg / ml.

II. <u>The Correlation between IL-6 and RF:</u>

An interesting finding that elevation of IL-6 accompanied by high RF titer which is clearly shown in figure 3. This figure shows that the majority of patients [65 out of 75] with a high IL-6 level [extends to about 600 pg/ml] are sero-positive for RF [i.e. > 20 IU/ml] while the minority of patients [10 out of 75] with very low IL-6 concentration are sero-negative for RF .

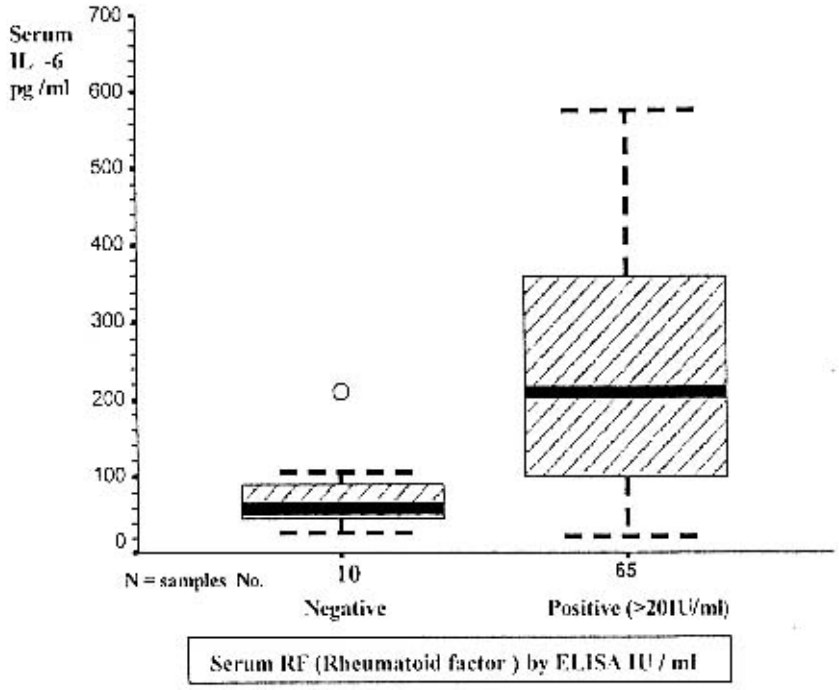

Figure 3. Correlation between IL-6 and RF in the sera of Rheumatoid Arthritis patients.

III. Correlation between IL-6 and HLA-DR4:

The current study shows that there is a prominent correlation between HLA-DR4 molecules and IL-6 concentration in the patient's sera as shown in the figure -4. This figure shows that the frequency of HLA-DR4 molecules are higher among patients with high IL-6 level [42] characterized by presence of HLA-DR4 molecules on the surfaces of their B cells while the others [33] whose sera apparent with low IL-6 concentration posses other DR molecules rather than DR-4.

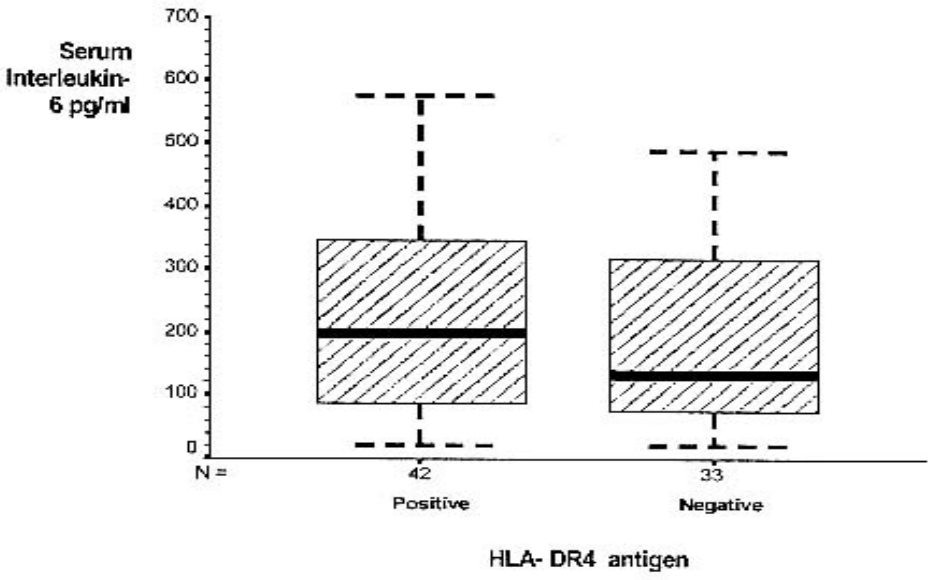

Figure 4. Correlation between IL-6 and HLA-DR4 alleles in rheumatoid arthritis

Discussion:

Studies are denoted that IL-6 was elevated in rheumatoid arthritis patients' synovial fluids as well as their sera [8-9]. The results of the current study have revealed an increasing in IL-6 level in RA patients sera in comparison with the control groups which is reckoned as an inflammatory mediator particularly among those patients with disease flare up. This result was comparable to [9-11]. The observed median level is 195 pg./ml which is higher than that of abroad (106 'p g:/ml).'[12]. This variation may be related to the variation in the duration of the disease and its activity particularly most the patients included in this study are at the acute stage of the disease flare up time [13-14]. Treated RA patients had displayed significantly reduced serum IL-6 (mean, 9.9 pg/ml) [15].

Moreover this study showed that there was a good correlation between IL-6 and RF levels, in which the later usually enhances the disease severity and may act in

synergetic fashion with IL-6. These findings were observed to be in consistent with that of [16], which revealed an association between IL-6 and other humoral inflammatory, disease activity parameters as CRP and ESR. Rheumatoid factor is considered as a prominent feature of RA and play a crucial role in RA pathogenecity [17]. The current study revealed a high correlation between RF and IL-6 which explains the role of RF in ICs formation, complement activation and finally cellular infiltration resulting in cytokine production [17]. It was denoted that the disease becomes worse in the presence of RF, HLA-DR4 molecules [signs of high disease activity], especially when they accompanied with elevation of IL-6 as shown by this study and other [18]. Sporadic patients are those with no familial history for RA , however, the frequency of HLA-DR4 was still higher than that for apparently healthy individuals [42 out of 75 RA patients].

This study demonstrated that (IL-6) is a protein overproduced in the sera of people with rheumatoid arthritis, where it's believed to be responsible for joint damage and swelling. Interleukin-6 may also be a cause of fever and excess blood platelets (thrombocytosis) in people with rheumatoid arthritis. Researchers hope that blocking IL6 can reduce the damage it does [19].

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