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Seasonal Fluctuations of Inflammatory Cytokines in Rheumatoid Arthritis Iraqi Patients

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ABSTRACT

Objective: This study aimed to evaluate the Seasonal variations of serum IL-6, IL-1β, IFN-γ and, ACCP autoantibodies in RA patients in Iraq.

Methods: The study included (45) patients with rheumatoid arthritis, who were selected with ages ranging between (20-60) years. The samples were collected and followed-up in cold, moderate and, hot seasons. This study was performed during the period from January 2019 to February 2020. They were selected from patients who were attending the outpatient Clinic in Medical City/Baghdad Teaching hospital/Rheumatology Unit. Data were collected using a questionnaire form. Anthropometric measurements were taken, and the other tests including the levels of IL-6, IL-1β, IFN-γ, and anti-CCP were quantified by using the ELISA technique.

Results: Serum levels of IL-6, IL-1β, and IFN-γ in RA patients were increased significantly ($p<0.05$) in winter as compared with moderate and summer seasons. While the levels of anti-CCP showed a significant increase ($p<0.05$) in the summer season compared with winter and moderate seasons.

Conclusions: winter weather has an important role in augmenting the severity of disease in RA patients due to its effects on inflammatory cytokines, while hot weather in the summer season affects more ACCP autoantibodies.

Key words: Cytokines, Inflammatory, Rheumatoid arthritis, Iraqi patients

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology, primarily affecting the synovial joints, characterized by a broad spectrum of extra-articular manifestations [1].

The clinical course of RA is variable, ranging from mild to severe disease, which can potentially lead to joint damage, chronic disability, and early mortality [2]. RA is characterized by persistent synovitis, systemic inflammation, autoantibody production, cartilage and bone destruction, leading to chronic disability and reduced life expectancy [3]. Pain, physical disability, fatigue, and sleep disturbances are some of the most pronounced symptoms in patients with a more severe disease progression or with longer disease duration, resulting in activity limitations that seriously affect their quality of life [4]. RA not only affects the joints and their associated structures, but it is also a disease with various extra-articular manifestations (scleritis, pleurisy, and vasculitis) [5].

Immunopathology of RA is characterized by a complex interplay between adaptive and innate immune elements, along with responses mediated by synovial resident cells. Indeed, the demarcation between these immunological compartments crosstalk's and integrate to form an inextricable network [6]. Induced citrullination of proteins can consequently cause a breach of peripheral immune tolerance to self-antigens, leading to inflammation and autoimmunity [7].

Cytokines such as interleukin 6 (IL-6) IL-17a, IL-22, IL-23, IL-1β, IL-8, IL-15, IL-18, IL-33, IL-37 interferon-γ (IFN-γ), tumor necrosis factor-a (TNF), granulocyte/macrophage colony-stimulating factor (GM-CSF), and granulocyte Colony-stimulating factor (G-CSF), are all detected either in the serum or in the synovial fluids of RA patients and play a specific role in the inflammatory processes [7-9].

MATERIALS AND METHODS

The study included (45) patients with rheumatoid arthritis, who were selected with ages ranging between (20-60) years. The samples were collected and followed-up in winter, moderate, and summer seasons during the period from January 2019 to February 2020. They were among those who attended the outpatients' Clinic in Medical City/Baghdad Teaching hospital/Rheumatology

Unit. Anthropometric measurements were performed and the questionnaire was applied for each patient. Tests were done in Medical City-Teaching Laboratories. Ethical approval and permission were taken from the committee of the Ministry of Health and assigned consent for each patient was documented before taken the blood for the research study.

Inclusion criteria

- Patients with a confirmed diagnosis of rheumatoid arthritis (RA) based on the 1987 American college of rheumatology criteria and Eular – ACR 2010 criteria [11].
- Patients in this study would be submitted to routine biochemical blood analysis tests.

Exclusion criteria

- Patients with hypertension and Diabetes mellitus.
- Pregnant and breastfeeding women.
- Patients with malignancy.
- Liver or renal disorders.
- Thyroid disorders.
- Other rheumatologic illness.
- Other endocrine disorders.

Five ml of venous blood was obtained from each patient aseptically from the cubital fossa, by vein puncture. Blood was transferred to a plain test tube and left to be coagulated and then centrifuged for 10 min at 3000 – 4000 rpm. Cooler boxes with ice packs at approximately 4° C, (2-8° C) were used for temporary storage and to facilitate the transport of samples to the laboratory. The resultant serum was used for measurement IL-1beta, IL-6, INFγ, and ACCP (MyBioSource, USA) by ELISA technique.

Statistical analysis

Statistical Package for the Social Sciences 20 for windows was used to analyze the quantitative data and expressed as mean ± standard error (M ± SE). One-way analysis of variance (ANOVA) was performed to analyze a difference among means of three groups (winter, moderate, and summer) session, if there are significant differences, they were analyzed by least significant difference (LSD) test. The P-value of differences < 0.05 was considered significant.

RESULTS AND DISCUSSION

There are seasonal variations in the levels of inflammatory cytokines, as IL-1β recorded a significant (P<0.05) increase in the cold season (50.89 ± 6.34) compared to the mild (34.66 ± 5.35) and hot season(12.15 ± 0.834) as well as the case for IL-6 and INFγ, which also recorded a significant (P<0.05) increase in the cold season compared to the moderate and hot seasons, and their results were according to the following sequence:

IL-6 (57.42 ± 7.48)(31.00 ± 5.86)(16.08 ± 1.60) and INFγ (177.73 ± 16.79) (134.79 ± 17.07)(75.81 ± 6.31).

On the contrary, ACCP recorded a significant (P<0.05) increase in the hot season (51.97 ± 7.60) when it was compared to the cold (12.71 ± 3.162) and temperate (9.90 ± 4.48) seasons. It should be noted that the levels of cytokines IL-1 β, IL-6, and INFγ, began to decline with the improvement of the weather, to record their maximum declines in the summer season Table1.

Table 1: Seasonal levels of inflammatory biomarkers(IL-1β IL-6, INFγ and ACCP in RA patients measured in pg./ml.

Parameters (pg./ml)	Winter Mean ± ER	Moderate Mean ± ER	Summer Mean ± ER	ANOVA P-value
IL-1β	50.89 ± 6.34	34.66 ± 5.35	12.15 ± 0.834	W vs M 0.020
				W vs S 0.001
				M vs S 0.001
IL-6	57.42 ± 7.48	31.00 ± 5.86	16.08 ± 1.60	W vs M 0.001
				W vs S 0.001
				M vs S 0.061
INFγ	177.73 ± 16.79	134.79 ± 17.07	75.81 ± 6.31	W vs M 0.036
				W vs S 0.001
				M vs S 0.004
ACCP	12.71 ± 3.162	9.90 ± 4.48	51.97 ± 7.60	W vs M 0.725
				W vs S 0.001
				M vs S 0.001

The biological mechanism for seasonal variations in RA activity remains to be elucidated. Since seasonality primarily concerns the length of daylight, solar effects on circadian rhythm, etc. all need to be considered. It has been suggested that there is a relationship between daylight and pro-inflammatory cytokine production [12,13]. Studies have shown that vitamin D intake and increased photosynthesized vitamin D are associated

with decreased risk of developing RA [14]. Researchers have concluded that less sunshine and less light may be the cause of RA activity exacerbation. Ishikawa and his colleagues demonstrated that serum vitamin D levels follow a lagged pattern relative to the astronomical seasons, peaking in summer and fall in winter [15], possibly as a result of fewer daylight hours and less outdoor activity because of cold weather. Vitamin D has immunomodulatory properties that down regulate activity of pro-inflammatory cytokines [16]. Low vitamin D levels may contribute to increased immune activation and may lead to RA development [17]. Several studies have reported vitamin D deficiency in RA patients, in up to 76% of patients and inverse association between vitamin D levels and disease activity [18]. However, evidence is controversial as reverse causation may explain some of these findings and a beneficial effect of vitamin D supplementation on RA disease onset has not been demonstrated.

Biological studies have always indicated that vitamin D has immunologic activities on multiple components of the innate and adaptive immune system [19,20], including increased IL-10 production, also inhibits inflammation by suppressing the expression of Toll-like receptor (TLR) and the production of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α) that play a crucial pathogenic role in autoimmune diseases [21]. In addition, 1, 25(OH) 2D promotes a tolerogenic state decreasing the synthesis of IL-12 and type 1 interferon (IFN) and enhancing that of IL-10 [22]. These suppressive immunologic properties have led to considering its role in autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, etc. In line with these observations, patients with RA show basal serum levels of 25(OH)D lower than healthy controls, and a negative correlation between serum 25(OH)D and RA disease activity was revealed by multiple studies [23,24]. Notably, vitamin D deficiency also appears as an environmental risk factor for RA [23].

The increasing number of findings support the idea that impaired vitamin D homeostasis contributes to autoimmune processes. These data can be presented as an explanation for part of the results obtained during the current study that explains the increased serum IL-1β, IL-6, and IFN-g during the winter season which can be attributed in part to a decreased level of Vitamin D. Several blood markers like fibrinogen, IL-6, and CRP showed seasonal variations with increases mostly in the cold season [25]. The mechanisms underpinning the pathogenesis of RA are varied, complex, and incompletely characterized. Nonetheless, an increasing body of evidence has identified inflammatory mechanisms in the lung, which has been linked to the production of ACPA, as events that precede the development of seropositive RA [26].

The bad environmental organization, low efficient technologies, and high traffic density resulted in new issues to be addressed, the air quality. . The large increase in the use of fossil fuels resulted in major air pollution episodes in many cities [27]. These factors together with a new and important factor exist in some developing countries including Iraq. These countries suffer from a lack of sufficient electricity availability for modern life. This condition caused high dependence on domestic generators to block the need for electricity shortage. These generators were additional effective and new factors for air pollution that increases man health for environmental hazards. It has been reported that those living in polluted environments had an increased risk of RA [28], and also pose a high risk of development of ACPA-seropositivity [29].

These data may provide a convincing explanation for the high levels of serum ACPA in patients in the highly polluted summer season in Iraq.

CONFLICT OF INTEREST

No conflict of interest.

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