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Leptin and Vascular Cell Adhesion Protein 1 as Physiological Biomarkers in Serum of Women Suffering from Rheumatoid Arthritis

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Abstract

BACKGROUND: Rheumatoid arthritis is defining as a common chronic and inflammatory disorder of systematic autoimmune disease. Leptin is a small peptide hormone involved in the inflammatory and immunomodulators processes of several diseases.

AIM: The study aimed at evaluating the level of leptin and Vascular Cell Adhesion Protein 1 (VCAM-1) and proves that they act as vital markers in the serum of rheumatoid arthritis.

MATERIALS AND METHODS: In this study, 80 serum samples from women were obtains (56 serum samples were distributing for women with rheumatoid arthritis and 24 serum samples for uninfected women who were considered a healthy group).

RESULTS: There are no significant difference in the concentration of the leptin hormone in the serum of both patients and healthy women, and that age, period, and severity of the disease had no effect on the level of leptin hormone. However, the results confirmed that at the probability level $p < 0.05$ the VCAM-1 concentration increased significantly in patients' serum when compared with the healthy group, and demonstrated that age groups only affected the VCAM-1 biomarker level.

CONCLUSIONS: Our current study concludes that leptin levels in the serum were not impacts by the inflammatory state in patients with rheumatism, whereas VCAM-1 level in rheumatic patients may be associate with inflammatory reactions.

Introduction

Rheumatoid arthritis is defining as a common chronic and inflammatory disorder of systematic autoimmune disease, affecting about 1% of the total population in the world [1]. Although the causes of the disease are unknown, many potential causes that led to the emergence of this disease have been detecting. Those causes are mostly related to oxidative stress, genetic and hormonal factors, viral and bacterial factors, and environmental triggers [2]. Rheumatoid arthritis is a general health condition and the most dangerous chronic disease due to its complications in the various body systems, including muscular and blood systems. It influences the eyes, heart, blood vessels, respiratory, and urinary systems of millions of people throughout the world and thus leads to increased costs of healthcare [3].

Leptin is a small peptide hormone having a molecular weight of 16 KDa. It contains 167 amino acids and its composition is similar to many cytokines with helical chains such as Interleukin (IL-6), IL-11, and IL-12. It represents a member of the Adipokines family, which consists of several compounds involved in the inflammatory and immunomodulators processes[4].

Leptin functions as an immunomodulator in the human body. It has been observing that there is an increased incidence of serious infection in people suffering from Genetic Leptin Insufficiency, and through immune deficiency during malnutrition and starvation when the concentration of leptin level is low [5]. Leptin contributes to autoimmune diseases, as is the case with rheumatoid arthritis. However, its role is still unclear because in many studies it has been proclaims that the circulation of leptin levels in the blood has been detected as either high or unmodified compared to leptin levels in the healthy group [6], [7]. The Vascular Cell Adhesion Protein 1 (VCAM-1) is a glycoprotein combined with a surfactant Sialoglycoprotein whose molecular weight is 110 KDa which belongs to the Immunoglobulin gene Superfamily and is one of the largest and most miscellaneous hosts of protein [8], [9]. The VCAM-1 adhesion molecule is mainly produce by endothelial cells, chondrocytes and synovial fibroblasts [10].

Due to the widespread adhesion molecules in human tissues and organs, participates in many physiological and pathological conditions such as autoimmune diseases, cardiovascular diseases, and inflammations [11]. The VCAM-1 adhesion molecule contributes importantly to the adhesion of cells with the

vascular endothelial tissue and their migration through it, and thus it causes the spread of cancer cells over new sites [12]. Likewise, the VCAM-1 takes part in the adhesion of leukocytes with the vascular endothelial tissue at the site of inflammation. In addition, it serves to transmit the signal between endothelial cells and white blood cells and contributes importantly to the development of rheumatism and arteriosclerosis [13].

The VCAM-1 adhesion molecule is closely associate with the process of generating new blood vessels (angiogenesis) in the tumor and metastasis. This process known to be governed by numerous factors like epidermal growth factor, vascular endothelial growth factor (VEGF), angiopoietin factor, hepatocyte growth factor, and others [14]. Ding *et al*. observed that tissues containing high concentrations of VCAM-1 have a higher vascular density than tissues with low VCAM-1 levels in patients suffering from gastric cancer [15]. The present study aims to shed light on the physiological relationship between leptin, VCAM-1 biomarkers, and arthritis disease.

Materials and Methods

Fifty-six samples of blood serum were obtains from women having rheumatoid arthritis. The samples were divide based on age groups into 18 blood serum samples for women aged between 20 and 35 years, 19 blood serum samples for women between the ages of 35 and 50 years, and 19 blood serum samples for women whose ages range from 50 to 65 years. Samples were obtains from the patients who attended the joint consultation at Basrah general hospital and some private clinics.

The healthy group: 24 samples of blood serum were obtains from healthy women after making sure that they did not have rheumatoid arthritis. The samples were dividing into three age groups corresponding to the age groups of patients, with an amount of 8 samples for each age group.

Preparation of serum: A 5mL of venous blood was obtained from the elbow by a clean medical syringe, and then the blood was place in a special gel tube and left for 20 min. Afterward, it was incubated in a centrifuge for 15 min at a rate 3000 rpm to obtain blood serum. The blood serum was dividing and placed in 1.5 mL Eppendorf tubes, and the samples were keeping in storage at −80°C in deep freeze until the tests were carrying out.

The leptin and the VCAM-1 concentration was identifying by the Enzyme-Linked Immuno-Sorbent Assay using the kits supplied by the American company of MyBioSource, and according to the method developed by (Jhon, 2000) [16] in measuring biomarker concentrations, the Sandwich technology, and the absorbance readings at a wavelength of 450 nm.

The statistical analysis of the values resulting from the data was performs by adopting the t-test and using the OneWay ANOVA analysis. The significance between the averages was assesses through the Least Significant Difference test at $p < 0.05$ and within the Standard Division using SPSS Ver. 21.

Results

The findings reported that there were no significant variances in the concentration of leptin hormone in rheumatoid arthritis (4440.80 Pg/mL) compared to the healthy group (4379.62 Pg/mL). Moreover, the statistical analysis did not reveal a significant variance in the leptin hormone concentration between the different age groups, the period, and the severity of the disease in rheumatoid arthritis patients, as shown in Table 1. Concerning VCAM-1 concentration, the findings of the present study reported that the concentration of VCAM-1 increased significantly in the patients' group having rheumatoid arthritis (18.12 Pg/mL) compared with the healthy group (11.75 Pg/mL). Moreover, the results, according to the age groups of patients, showed also significant differences between the three age groups, as the rate in the first age group was (16.50 Pg/mL ± 2.74), and in the second age group was (18.84 Pg/mL ± 3.27). The rate in the third age group was 19.21 Pg/mL ± 2.76. The different letters (a, b) indicate that there were significant differences between the groups at ($p < 0.05$). However, the duration and severity of the disease did not show any significant effect on the level of the VCAM-1 biomarker in rheumatoid arthritis patients, as shown in Table 2.

Table 1: Concentration of leptin hormone

Variables	No.	Mean ± SD pg./mL	p value
Participants			
RA	56	4440.8 ± 468.9	0.607
Healthy people	24	4379.62 ± 521.36	
Age (years)			
20–35	18	4442.5[a] ± 824.12	ns
35–50	19	4412.63[a] ± 617.76	
50–65	19	4467.36[a] ± 804.66	
The period of the disease			
1 month–3 years	26	4494.65 ± 609.6	0.516
3 years–20 years	30	4394.13 ± 539.78	
Severity			
Severe	16	4026.25[a] ± 1018.88	ns
Moderate	32	4685.5[a] ± 494.12	
Mild	8	4291.12[a] ±549.38	

The similarity of the letters indicates that at ($p < 0.05$) there are no significant differences, and the similarity of the letters indicates no significant difference at ($p < 0.05$).

Discussion

Leptin is known for its pro-inflammatory activity which is performed by activating monocytes and

Table 2: Concentration of VCAM-1

Variables	No.	Mean ± SD pg./mL	p value
Participants			
RA	56	18.12 ± 3.20	0.0001
Healthy people	24	11.75 ± 3.42	
Age (years)			
20–35	18	16.50[a] ± 2.74	ns
35–50	19	18.84[b] ± 3.27	
50–65	19	19.21[b] ± 2.76	
The period of the disease			
1 month–3 years	26	17.76 ± 2.47	0.444
3 years–20 years	30	18.43 ± 3.73	
Severity			
Severe	16	17.50[a] ± 4.14	ns
Moderate	32	18.56[a] ± 2.90	
Mild	8	17.62[a] ± 2.06	

The similarity of the letters indicates that at ($p < 0.05$) there are no significant differences, and the similarity of the letters indicates no significant difference at ($p < 0.05$).

macrophages to generate more inflammatory cytokines (such as IL-6 and Tumor Necrosis Factor [TNFα]) [17]. Due to this effect generated by leptin, the concentrations of the leptin serum in rheumatoid patients are expecting to increase, which is inconsistent with what we have observed from the results of our current study [18].

The deficiency of genetic leptin increases the severity of inflammatory infections in humans. It has been proven that there are many severe infections in rheumatism patients in comparison with general people, particularly patients who are recipients of antitumor necrosis factor (anti-TNF) treatment. This indicates that leptin concentration is suppressing by chronic inflammation, which may contribute to an increased incidence in rheumatic patients [19].

The results of the current study investigating women with rheumatoid arthritis showed no significant differences in leptin concentration in the serum of patients and healthy people. In addition, the results of our study agreed with the findings of several other studies which reported that leptin concentrations in both patients and healthy subjects were similar [20], [21]. The reason can be ascribed to the fact that the patients did not receive Methotrexate (MTX) treatment, since this treatment stimulates the hypothalamus to produce leptin in patients. This has been confirming by an earlier study conducted by Bokarewa *et al*. which reported a significant rise in the level of leptin in the patients' serum, who are treated by MTX, compared with untreated patients [22].

Information – gained from various studies – about the contribution of leptin to rheumatoid arthritis and other rheumatic diseases are incongruous. The findings are agreeing with many other studies such as Targońska-Stepniak *et al*. [23], Toussirot *et al*. [24], have shown leptin concentrations are similar in the serum of patients and the serum of healthy people. However, the results obtained from another study [25], have reported either lower leptin concentrations in patients' serum in comparison with healthy people, or high leptin concentrations in patients' serum compared with healthy people, as observed by many studies exploring patients with rheumatism and osteoporosis [17], [26]. The reason can be ascribed to a range of factors. These factors include the large proportion of rheumatism patients whose inflammatory parameters were not high at the time of examination. The higher BMI of the patient group compared with healthy people. The patients being in the period of chronic inflammation, as it has been report that leptin levels increase during acute inflammation and do not increase during chronic inflammation in various inflammatory diseases [27], [28].

The other goal of our research is to evaluate the relationship between leptin concentration in patients' serum according to age, duration, and severity of the disease. Our study did not report significant differences among leptin concentrations concerning these three variables. The results of our study agreed with the results of several studies [28], [29], while a study by Bokarewa *et al*. [22], have observed that leptin concentration gradually increased in the serum along with the progressive duration of the disease.

As for VCAM-1, VCAM-1 is considered an essential molecule of adhesion that assists the connection and link of white blood cells with each other or with other tissues, and then their transmission through the endothelial tissue. Thus, it has a significant role in pathological and physiological processes, including increasing the density of white blood cells and vascular cells, immune cell differentiation, invasion, and metastasis of tumor, transduction of intracellular signal and autoimmune diseases [30], [31]. As a chronic inflammatory disease, rheumatoid arthritis can be linked to an elevated level of this adhesion molecule. However, studies exploring changes in VCAM-1 levels and their connection with developing rheumatism are still scaring]32[.

Our study's results reported that the concentration of VCAM-1 increased significantly among patients and healthy people. Our results agreed with earlier studies [33], [34], which confirmed a raise in the adhesion molecules levels in the patient's serum and that the adhesion molecules contribute importantly to developing rheumatism.

In his study, Wang *et al*. [35], observed a rise in levels of VCAM-1 in the rheumatoid patients' serum, and that this raise persisted for a short period while patients were under conventional treatment. He also noted that some clinical symptoms decreased with the continuation of treatment, and then the levels of Rheumatoid Factors (RFs) decreased in the serum. Their decrease was accompanying by the gradual decreases of adhesion molecules, indicating the association of VCAM-1 with the disease status and levels of RFs. Similarly, Klimek *et al*. [36], studying serum samples of 29 rheumatic patients (22 women and 7 men), reported that the concentrations of VCAM-1 increased significantly in rheumatoid patients' serum compared with healthy people.

Smith *et al*. [37] explored the impact of anti-rheumatoid therapies like MTX and others on patients having rheumatoid arthritis. That observed that the level

of VCAM-1 decreased in the treated group of patients in comparison with the rheumatoid patients who had not been treating. Another study, whose results were contrary to our study's results, demonstrated that the adhesion molecules levels were lower in rheumatism patients in comparison with healthy people [38].

As regard the relationship between VCAM-1 concentration and age, period, and severity of the disease, the results of our study revealed significant differences between the three different age groups. However, our study did not reveal significant differences between the degrees (severe, moderate, and mild) of the disease severity. In addition, our results showed no significant differences between the first and second periods of the disease. The results of our current study agreed with the results of other studies which showed that there is no correlation between sex, age, disease period, and between the concentrations of adhesion molecules (VCAM-1, Intercellular adhesion molecule 1, E-selectin) and the VEGF [33], [38].

Conclusion

Our current study concludes that the concentrations of leptin in the serum were not affecting by the inflammatory state in patients with rheumatism. Concerning VCAM-1, we observed that disturbances in the VCAM-1 biomarker level for patients having rheumatism may be links to autoimmune diseases and inflammatory reactions. These increased levels of adhesion molecules can help predict therapeutic effects and can be used as a vital indicator for monitoring the disease.

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Ethics Approval and Consent to Participate

This research was approved by the Basrah University – Iraq. Serum was obtained from patients at Basrah general hospital after their consent by filling out a questionnaire.

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