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SERUM LEVELS OF ADIPONECTIN BEFORE AND AFTER ADMINISTRATION OF ANTI-TUMOR NECROSIS FACTOR AGENTS IN IRAQI PATIENTS WITH RHEUMATOID ARTHRITIS

ABDUL-WAHID K.M.[1], AL-DERZI A.R.[1], AL-OSAMI M.H.[2] AND AL-ANI M.M.[1]*

[1]Department of Microbiology & Immunology, College of Medicine, Baghdad University, Baghdad, Iraq.
[2]Department of Rheumatology & Medical Rehabilitation, College of Medicine, Baghdad University, Baghdad, Iraq.
*Corresponding Author: Email- misk62@yahoo.com

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Abstract- Rheumatoid arthritis is a chronic systemic inflammatory disease that affects many organs and tissues and principally attacks synovial joints. It is an autoimmune disease that produces inflammatory response of synovium secondary to hyperplasia of the synovial cells. Recent findings suggest that adiponectin may be involved in the pathogenesis of rheumatoid arthritis (RA), however levels of adiponectin in synovial fluid and sera were elevated in patients with RA. Thus, it was suggested that adiponectin can exert significant proinflammatory and matrix-degrading effects. The aim of this study was to evaluate the serum levels of adiponectin before and after administration of anti-tumor necrosis factor agents in Iraqi patients with rheumatoid arthritis.

This study was conducted in the period between November 2012 and April 2013 gathering a total sum of seventy five (75) subjects. Forty five (45) of them (patient group) were diagnosed as established RA patients who were attending the rheumatology out patient clinic of Baghdad teaching hospital. Thirty (30) patients of them were on traditional treatment (steroid and/or cytotoxic drugs), while the other fifteen (15) patients were already stopped traditional treatment for at least one month to be given the biological (anti-TNF) treatment, and whom were followed one month later after giving the biological treatment. Mean serum level of adiponectin was statistically higher in patient group (45.00±37.15 ug/dl) than control group (20.56±16.91 ug/dl), but there was no statistical differences in the mean serum level of adiponectin between patients receiving traditional treatment and those receiving biological treatment, nor before and after biological treatment. The serum levels of adiponectin were higher in patient group than control group, so adiponectin can act as a proinflammatory cytokines in patients with RA.

Keywords- Rheumatoid arthritis, adiponectin, TNF, anti-CCP

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Introduction

Rheumatoid arthritis (RA) is considered the most common chronic inflammatory autoimmune disease, occurring in 1 to 2% of the worldwide population. The hallmark of rheumatoid arthritis consists of synovial joint inflammation, leading to bone and cartilage destruction. Extra-articular manifestations, including rheumatoid nodules, vasculitis, lymphadenopathy, cardiopulmonary disease and eye inflammation, may also occur [1]. RA is a multifactorial disease that results from interactions between genetic and environmental factors, while personal and lifestyle factors influence the course of the disease [2]. The predominance of RA in females suggests a role for hormonal factors due to the stimulatory effects of estrogens on the immune system, because estrogen inhibits the function of T-suppressor cell and at the same time enhances the function of T-helper cell, although low testosterone levels have been reported in men with RA [3]. Among environmental factors, smoking has by far the strongest association with RA, however smoking increases susceptibility to RA and adversely affects the clinical course of the disease, as shown by cross sectional and longitudinal studies [4].

One key inflammatory cascade includes overproduction and overexpression of TNF [5].This pathway drives both synovial inflammation and joint destruction, however TNF overproduction has several causes, including interactions between T and B lymphocytes, synovial-like fibroblasts, and macrophages, although this process leads to overproduction of many cytokines such as interleukin 6, which also drives persistent inflammation and joint destruction [6].

Many auto-antibodies could be implicated in the pathogenesis of the disease, rheumatoid factor interact with the Fc portion of IgG, however the major isotype is IgM but IgG-RF and IgA-RF are also present in the serum and synovial fluid of patients with RA and may provide additional diagnostic information, although RF can be measured by various methods including agglutination techniques such as the classical Waaler-Rose test and ELISA, with the latter being able to distinguish between RF subtypes [7].

It is now definitely established that ACPA are the most specific serological marker antibodies for RA, moreover, as with RF, they are present early in the course of the disease and may even precede clinical onset [8]. ACPA can be measured by ELISA which may use citrullinated proteins such as filaggrin, vimentin or fibrinogen or citrullinated peptides as antigen, however the currently most widely used assays employ a cyclic citrullinated peptide (CCP); ACPA determined by such assays (available commercially from several manufacturers) are usually referred to as anti-CCP antibodies [9].

The important role of adipokines in inflammation provides novel links between adipose tissues, adipokines, and inflammatory- related disorders, including RA, thus attracting the interest of both basic researchers and clinical physicians. Recent findings have demonstrated that adipokines exert potent modulatory actions on tissues and cells involved in RA, including cartilage, synovium, bone, and various immune cells [10]. Compared with other adipokines, the circulating concentrations of adiponectin in normal healthy subjects are surprisingly high, with the mean value ranging between 0.5 and 30 mg/L, accounting for about 0.01% of all plasma proteins in humans and 0.05% in rodents, respectively [11].

Rho, et al [12] showed that the serum concentrations of adiponectin, visfatin, the C-reactive protein (CRP), and TNF-a were significantly higher in RA patients than in controls. Moreover, this association remained significant even after adjusting for body mass index (BMI), inflammation, or both. Furthermore, disease duration correlated significantly with adiponectin concentrations.

However, Klein-Wieringa, et al [13]. demonstrated that levels of IL-6, TNF-a, visfatin, and adiponectin were positively associated with radiographic progression. They concluded that baseline serum adiponectin levels could predict radiographic progression in early RA.

Serum adiponectin levels correlated positively with age, disease duration, and high-density lipoprotein cholesterol (HDL) levels. While in patients with long-standing RA, there was a negative correlation between adiponectin and numbers of tender, swollen joints, however, another study suggested that although both the serum and the synovial fluid have higher adiponectin concentrations, this was not related to age, disease duration, body mass index, or disease activity in RA patients [14].

Interestingly, Yoshino, et al [15] reported that female RA patients had significantly higher serum adiponectin concentrations than normal female control subjects, but this difference was not observed in males. However, other groups have shown that serum adiponectin concentrations did not differ significantly between men and women [16].

Subjects and Methods

This study was conducted in the period between November 2012 and April 2013 gathering a total sum of seventy five (75) subjects. Fourty five (45) of them (patient group) were diagnosed as established RA patients who were attending the rheumatology out patient clinic of Baghdad teaching hospital. There were thirty two (32) females to thirteen (13) males with ratio of female to male was 3.5:1, their age ranged between 20-68 years with a mean age 43.73±12.24 years. Thirty (30) patients of them were on traditional treatment steroid and/or cytotoxic drugs, while the other fifteen (15) patients were stopped the traditional treatment for at least one month to be given the biological (anti TNF) treatment, and whom were followed after one month after giving the biological treatment. Also this study included thirty (30) subjects who were apparently healthy (control group) twenty two (22) of them were female and eight (8) were males with a ratio of female to male was 3.75:1 and their ages ranged between 20-54 years with a mean age 43.37±10.76 years. From each subject 5ml of venous blood was aspirated and centrifuged to separate the serum after well explanation and full agreement to be included in the research voluntary. The sera were stored at -20C and tested for anti-CCP and adiponectin level using enzyme linked immunosorbent assay (ELISA) kit. Statistical analysis in this study was done according to SPSS version 17.

Results

This study was included forty five (45) patients with RA, thirty two (32) females & thirteen (13) males, the female to male ratio was 3.5:1, with mean age was 43.73 ± 12.24 years years and 30 healthy subjects, their mean age was 43.37 ± 10.76 years.

Latex agglutination test of RF, was positive in only thirteen patients (28.8%), and was positive in seven subjects (23.3%) from control group, C- reactive protein: (CRP) was positive in thirty six patients (80.0%), and was positive in nine subjects (30.0%) from the control group, and Anti-CCP: was positive in thirty two patients (71.1%), and was positive in one subject (3%) of control group as shown in [Table-1].

Table 1- Results of latex agglutination test of RF,CRP and Anti-CCP in patient and control groups

Parameter	Result	Patient (N=45)	Control (N=30)	*p*-Value
RF	Positive	13 (28.8%)	7 (23.3%)	0.79
	Negative	32 (71.2%)	23 (76.7%)	Not sign
CRP	Positive	36 (80%)	9 (30%)	<0.0001
	Negative	9 (20%)	21 (70%)	Highly sign
Anti-CCP	Positive	32 (71.1%)	1 (3%)	<0.0001
	Negative	13 (28.9%)	29 (97%)	Highly sign

Results of latex agglutination test of RF, CRP and Anti-CCP in fifteen (15) patients before and after biological treatment was statistically not significant as shown in [Table-2].

Table 2- Results of latex agglutination test of RF,CRP and Anti-CCP in patients before and after biological treatment

Parameter	Result	Before biological treatment (N=15)	After biological treatment (N=15)	*p*-Value
RF	Positive	3 (20%)	3 (20%)	1
	Negative	12 (80%)	12 (80%)	Not sign
CRP	Positive	13 (86.6%)	13 (86.6%)	1
	Negative	2 (13.4%)	2 (13.4%)	Not sign
Anti-CCP	Positive	13 (86.6%)	12 (80%)	1.000
	Negative	2 (13.4%)	3 (20%)	Not sign

Serum levels of adiponectin (ug/dl): Using ELISA technique, the mean serum level of adeponectin (ug/dl) was higher in patient group (45.00±37.15) than control group (20.56±16.91) and this difference was statistically highly significant (P value =0.001) as shown in [Table-3].

[Table-4] showed that serum level of adeponectin (ug/dl) was higher in patients who received biological treatment, than in patients treated with traditional types of treatment and the difference was statistically not significant (P value =0.289).

[Table-5] showed that the mean serum level of adiponectin (ug/dl) among fifteen patients after biological treatment was higher than before biological treatment and the differences was statistically not significant (*p* value =0.83).

Table 3- Results of serum levels of adiponectin (ug/dl) in patient and control groups

Group	Patients	Controls
Number	45	30
Mean (ug/dl)	45	20.56
Standard deviation	± 37.15	± 16.91
SEM	5.53	3.08
T-Test	3.37	3.37
Df	73	73
p-value*	0.0012	0.0012
**Highly statistically significant*		

Table 4- Results of serum levels of adiponectin (ug/dl) in patients without treatment, and patients treated with traditional types of treatment

Group	After Biological Treatment	After Traditional Treatment
Number	15	30
Mean (ug/dl)	53.39	40.8
Standard deviation	±43.76	±33.39
SEM	11.29	6.09
1.0735		T-Test
43		Df
0.289		*p*-value*
**Not statistically significant*		

Table 5- Results of serum level of adiponectin (ug/dl) in same patients before and after biological treatment

Group	Before Biological Treatment	After Biological Treatment
Number	15	15
Mean (ug/dl)	50.23	53.39
Standard deviation	± 38.06	±43.76
SEM	9.82	11.29
0.211		T-Test
28		Df
0.83		*p*-value*
**Not statistically significant*		

Discussion

RA is a common inflammatory disorder manifesting typically as a symmetrical polyarthritis, it is characterized by chronic inflammation of synovial joints that leads to progressive joint destruction & disability with reduction in quality of life [17]. This study included forty five (45) patients with RA who attended the rheumatology outpatient clinic of Baghdad teaching hospital in the period between November 2012 to April 2013 fifteen (15) of them followed up after one month after giving biological treatment and thirty (30) control healthy person. The mean age of patients was 43.73 ± 12.24 years, this is in accordance with other studies which mentioned that RA affects usually people who are more than 40 years of age & starts usually after middle age [18]. RA starts after 40 years due to many reasons that depress immunity as stress, thymic depression, exposure to different antigens as smoking (tobacco) that leads to activation of auto-reactive lymphocyte [19]. This study shows that females are more predominant for RA than males with a ratio of 3.5:1 and this agree with other studies that showed a ratio of 3:1 conducted by Al-Rawi, et al [20]. The female predominance could be due to hormonal factors such as estrogen which enhances the function of T-helper cells and inhibits the function of T-suppressor cells [21].

Anti-CCP antibodies combine high specificity for the diagnosis of RA [22,23]. They have superior diagnostic performance in early and undifferentiated arthritis. They show a great promise as a diagnostic marker of RA as they can be detected very early in RA and they may predict the eventual development into RA. They have also shown the ability to distinguish between erosive and non erosive disease, making them a good prognostic marker [24].

In the present study Anti-CCP was positive in thirty two patients (71%), and was positive in only one subject (3%) of control group as shown in [Table-1], this reflects high sensitivity (71%) and high specificity (97%). This is in accordance with the study conducted by Ammar at 2012 which mentioned a sensitivity and specificity 66% and 100% respectively [8].

Results from [Table-2] revealed that patients before biological treatment had higher proportion of Anti-CCP positivity (86%), than patients after biological treatment (80%) which was statistically not significant [25]. Recent study however, indicate that anti-TNF alpha treatment in RA results in a decrease in the serum titers of anti-CCP antibodies in patients showing clinical improvement, suggesting that these measurements may be a useful adjunct in assessing treatment efficacy [26].

In the present study the mean serum level of adiponectin of patients with RA (45.00ug/dl) was higher than those in control subjects (20.56ug/dl) as shown in [Table-3]. Thus serum levels of adiponectin are reported to be higher in patients with RA than in healthy controls [27] and it is suggested that adiponectin could be proinflammatory *in vitro* [28].

The results from [Table-4] revealed that the mean serum level of adiponectin in patients treated with biological agent (53.39ug/dl) was higher than those treated with traditional treatment (40.80ug/dl), and the results from [Table-5] revealed that the mean serum level of patients after biological treatment (53.39ug/dl) was higher than those before biological treatment (50.23ug/dl), though statistically not significant, this is because that TNF and adiponectin mutually inhibit the production of each other in adipose tissue [29], therefore, blockage of the action of TNF by anti-TNF agents is a reasonable explanation. Alleviation of joint inflammation *per se* by treatment might be another explanation for the increase in plasma adiponectin [30]. This increasing level of adiponectin in patients with RA could be protective against cardiovascular diseases in those patient so it may beneficial for them [14,31].

Conflict of Interest : None declared.

References

[1] Firestein G.S. (2005) *Textbook of Rheumatology*, 7th ed., Saunders Elsevier, Philadelphia.

[2] Silman A.J., Mac Gregor A.J., Thomson W. (1999). *Br. J. Rheumatol.*, 903-907.

[3] Cutolo M., Villaggio B., Craviotto C., Pizzorni C., Seriolo B., Sulli A. (2002) *Autoimmun. Rev*., 1, 284-289.

[4] Costenbader K.H., Manson J.E. (2008) *Arthritis Rheum*., 59, 299-301.

[5] Feldmann M., Brennan F.M., Maini R.N. (1996) *Cell*, 85, 307-10.

[6] Choy E.H., Panayi G.S. (2001) *N. Engl. J. Med*., 344, 907-916.

[7] Jacobsson L.T., Turesson C., Nilsson J.A. (2007) *Ann. Rheum. Dis*., 66, 670-675.

[8] Ehling A., Schaffler A., Herfarth H. (2006) *J. Immunol*., 176, 4468-4478.

[9] Klareskog L., Ronneild J., Lunderburg K. (2008) *Annu. Rev. Immunol*., 26, 651-675.

[10] Gomez R., Conde J., Scotece M., Gomez-Reino J.J., Lago F., Gualillo O. (2011) *Nature Reviews in Rheumatology*, 7, 528-536.

[11] Sun Y., Xun K., Wang C., Zhao H., Bi H., Chen X. (2009) *Cardiovascular Therapy*, 27, 59-75.

[12] Rho Y.H., Solus J., Sokka T., Oeser A., Chung C.P., Gebretsadik T. (2009) *Arthritis and Rheumatism*, 60, 1906-1914.

[13] Klein-Wieringa I.R., van der Linden M.P., Knevel R., Kwekkeboom J.C., van Beelen E., Huizinga T.W. (2011) *Arthritis and Rheumatism*, 63, 2567-2574.

[14] Senolt L., Pavelka K., Housa D., Haluzik M. (2006) *Cytokine*, 35, 247-252.

[15] Yoshino T., Kusunoki N., Tanaka T., Kaneko K., Kosonoki Y., Kawai S. (2011) *Inter. Med*., 50, 269-275.

[16] Targonska-Stepniak B., Dryglewska M., Majdan M. (2010) *Rheumatology International*, 30, 731-737.

[17] Silman A.J. and Pearson J.E. (2002) *Arthritis Res*., 4(3), S265-S272.

[18] Alamanos Y., Voulgari P.V. (2006) *Semin. Arthritis. Rheum*., 36 (3), 182-188.

[19] Kotzin B.L. (2005) *J. Rheematol. Suppl*., 73, 14-18.

[20] Al-Rawi Z.S., Al-Shackarchi H.A., Marjana N.H., Hart F.D. (1977) *Rheumatology*, 16(2), 128-132.

[21] Ahmed S.A., Dauphinee M.J., Talal N. (1985) *The Journal of Immunology*, 134(1), 204-210.

[22] Smeets T.J., Kraan M.C., Van Loon M.E. and Tak P.P. (2003) *Arthritis Rheum*., 2155-2162.

[23] Roll P., Muhammad K., Schumann M., Kleinert S., Tony H.P. (2012) *Scand. J. Rheumatol*., 41(3), 180-185.

[24] Kastbom A. (2004) *Ann. Rheum.* Dis., 63, 1085-1089.

[25] da Mota L.M., dos Santos Neto L.L., Pereira I.A. (2010) *Acta. Reumatol. Port*., 35(2), 156-166.

[26] Vanichapuntu M., Phuekfon P., Suwannalai P. (2010) *Rheumatol. Int*., 30(6), 755-759.

[27] Otero M., Lago R., Gomez R., Lago F., Dieguez C., Gomez-Reino J.J. (2006) *Annals of Rheumatic Diseases*, 65, 1198-1201.

[28] Ehling A., Schaffler A., Herfarth H., Tarner I.H., Anders S., Distler O. (2006) *Journal of Immunology*, 176, 4468-4478.

[29] Maeda N., Shimomura I., Kishida K. (2002) *Nat. Med*., 8, 731-737.

[30] Lo J., Bernstein L.E., Canavan B. (2007) *Am. J. Physiol. Endocrinol. Metab*., 293, E102-E109.

[31] Xu A., Chan K.W., Hoo R.L. (2005) *J. Biol. Chem*., 280, 18073-18080.