SERUM ADIPONECTIN AND BODY COMPOSITION PARAMETERS IN PATIENTS WITH RHEUMATOID ARTHRITIS: RELATIONSHIP WITH DISEASE ACTIVITY

ROMATOİD ARTRİTLİ HASTALARDA SERUM ADİPONEKTİN VE VÜCUT KOMPOZİSYONU PARAMETRELERİNİN HASTALIK AKTİVİTESİ İLE İLİŞKİSİ

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ABSTRACT

INTRODUCTION: Rheumatoid arthritis is a progressive inflammatory disease which results in swelling and tenderness in joints due to progressive destruction of joint tissue. Adiponectin is synthesized by the adipose tissue and at least some isoforms have been shown to display pro-inflammatory properties and also adiponectin was reported to have an important affect in rheumatoid arthritis pathophysiology. We believe that studies are lacking in terms of comparing a broad range of body composition measurements and quality of life scores with other disease parameters. In our study we aim to investigate the relationship between these parameters in rheumatoid arthritis patients.

MATERIALS AND METHODS: Fifty-five patients (11 males, 44 female) who applied to our center with an rheumatoid artritis diagnosis were included to the study. Patients' disease parameters, disease activity scores, anthropometric measurements, body composition parameters, serum adiponectin levels and disease parameters quality of life survey results were recorded. The presence of metabolic syndrome was also assessed and saved.

RESULTS: Adiponectin was positively correlated with body fat (%) and fat mass index (FMI), and negatively correlated with fat-free mass (%). No significant correlations were found between adiponectin levels and other disease parameters. Furthermore, none of the disease parameters showed any remarkable association with anthropometric measurements and body composition results, apart from a significant negative correlation between RA-QoL and fat-free mass. A surprising finding of the study was the fact that disease duration was significantly shorter in patients with metabolic syndrome.

CONCLUSION: Multifactorial pathogenesis between adiponectin isoform measurements and disease activity status should be considered in the evaluation of adiponectin and related parameters Future studies comprising patients with different disease activity may explain conflicting results.

Keywords: *Rheumatoid arthritis, metabolic syndrome, Adiponectin, quality of life*

ÖZET:

GİRİŞ: Romatoid artrit eklem dokusunun ilerleyici yıkımı nedeniyle eklemlerde şişme ve hassasiyetle sonuçlanan ilerleyici inflamatuar bir hastalıktır. Adiponektin, adipoz dokudan sentezlenir ve bazı izoformların pro-inflamatuar özellikleri gösterdiği ve adiponektinin romatoid artrit patofizyolojisinde önemli bir etkiye sahip olduğu bildirilmiştir. Çeşitli vücut kompozisyonu ölçümleri ve yaşam kalitesi skorlarının diğer hastalık parametreleri ile ilişkisini inceleyen çalışmaların eksik olduğuna inanıyoruz. Çalışmamızda romatoid artrit hastalarında bu parametrelerin ilişkisini incelemeyi hedefledik.

MATERYAL-METHOD: Çalışmaya romatoid artrit tanısı ile merkezimize başvuran 54 hasta (11 erkek, 44 kadın) dahil edildi. Hastaların hastalık parametreleri, hastalık aktivite skorları, antropometrik ölçümleri, vücut kompozisyon parametreleri, serum adiponektin düzeyleri ve hastalık parametrelerinin yaşam kalitesi anket sonuçları kaydedildi. Metabolik sendrom varlığı da değerlendirildi ve kayıt edildi.

SONUÇLAR: Adiponektin ile vücut yağı (%) ve yağlı vücut kitlesi arasında pozitif korelasyon ve yağsız vücut kitlesi (%) arasında ise negatif korelasyon vardı. Adiponektin düzeyleri ile diğer hastalık parametreleri arasında anlamlı ilişki bulunamadı. Ayrıca, RA-QoL ve yağsız kütle arasındaki anlamlı negatif korelasyon dışında, hastalık parametrelerinin hiçbiri antropometrik ölçümler ve vücut kompozisyonu sonuçları ile belirgin bir ilişki göstermedi. Çalışmanın şaşırtıcı bir bulgusu metabolik sendromlu hastalarda hastalık süresinin anlamlı olarak daha kısa olmasıydı.

SONUÇ: Adiponektin izoform ölçümleri ve hastalık aktivitesi durumu arasındaki multifaktöriyel patogenez, adiponektin ve ilgili parametrelerin değerlendirilmesinde dikkate alınmalıdır. Farklı hastalık aktivitesine sahip hastaları içeren gelecekteki çalışmalar çelişkili sonuçları açıklayabilir.

Anahtar kelimeler: *Romatoid artrit, metabolik sendrom, adiponektin, yaşam kalitesi*

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INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune, inflammatory disease which progresses with irreversible erosive tissue destruction of the joints and is characterized by persistent synovial inflammation and hyperplasia (1). In developed countries, its prevalence is reported between 0.5-1% in adults and studies indicate that the frequency is on the rise. It is up to 3-to-5 times more frequent in females compared to males (2, 3). Although the etiology of RA is yet to be identified; environmental, genetic, and hormonal factors are believed to contribute to the development of the disease (3). Many factors thought to be associated with its development have been discussed.

One such factor is the possibility of an association with RA and changes in body composition. This may be an important suggestion, because various studies have drawn attention to android fat deposits when evaluating the cardiovascular risks of patients with chronic inflammatory diseases (4, 5). Android fat deposits are termed as visceral fat in the abdominal region (6). It has been previously shown that, visceral fat (rather than subcutaneous fat) is an important predictive factor for cardiovascular events (7). Thus, the evaluation of android/visceral fat deposits may be important for patients with chronic inflammatory diseases such as RA. Additionally, adipose tissue is not merely a depot organ, it is an important contributor to metabolism via the synthesis of countless adipokines, such as leptin, adiponectin, resistin, and visfatin (8).

Adiponectin is synthesized in adipocytes and affects the glucose and lipid metabolisms. It has been shown to be greatly increased in the serum and synovial fluid of patients with RA (9). Various studies have shown that reduced adiponectin levels are associated with type 2 diabetes, atherosclerosis, and metabolic syndrome; thus it is used as a biomarker in these diseases (10, 11). Available evidence suggests that adiponectin may increase inflammation in RA and may contribute to erosive joint damage. Therefore, adiponectin may have a potential as a biomarker of RA (12, 13).

In the light of these data, it was concluded that adiponectin might play a crucial role in the pathogenesis of RA. Investigation of adiponectin levels and adipose tissue distribution may contribute to the treatment of RA and may be used adjunct to disease activity parameters such as DAS28-ESR and DAS28-CRP. The aim of this study was to determine serum adiponectin levels and body composition in a group of patients with RA and to investigate any relationships between these parameters.

MATERIALS- METHODS

Study group

All patients who applied to our clinic from June 2015 to July 2016 were considered as candidates for the current cross-sectional study. In the mentioned period, 77 RA patients who met American College of Rheumatology 2010 classification criteria applied to our clinic, we excluded 6 patients due to having a carcinoma diagnosis, 4 patients due to having prosthetic-metallic elements or internal pacemaker, 8 patients due to rejecting to participate in the study, 2 patients due to pregnancy. Thus, a final total of 55 patients were included in the study.

Ethical issues

Ethical approval was obtained from Clinical Research Ethical Committee. All patients gave informed consent. Additionally, all processes of the study were conducted according to the Helsinki Declaration and Good Clinical Practice guideline. Measurements

The demographic and clinical variables of the patients (age, sex, body mass index (BMI), duration of disease, comorbidities, medications) were determined. BMI is calculated by dividing body weight with the square of subject height (in meters). Disease activity parameters (DAS28-ESR, DAS28-CRP, functional status assessed by Health Assessment Questionnaire (HAQ) and quality of life (QoL) assessed by RA-QoL questionnaires) were recorded. The DAS28 scores (ESR and CRP) are calculated by determining the number of tender and swollen joints in addition to ESR or CRP values in patients with RA (14). The HAQ is a widely accepted and validated self-reported survey used to determine health and functional status (32). The RA-QoL questionnaire is also a self-reported survey that was specifically designed to determine the health status of RA patients. The RA-QoL includes the following subsections: daily living, social interaction/function, emotions, mood and recreation, pastimes, and physical contact (33). Serum adiponectin levels were determined by ELISA tests and body composition parameters (fat mass (FM), fat-free mass (FFM)) were determined by multi-frequency bioelectrical impedance analysis (Scan plus 950 body composition analyzer-Jawon Medical Co. Ltd. Kyungsan city, Korea). Anthropometric measurements (weighy, height, circumferences of waist (WC), mid- upper arm (MUAC), calf (CC) and neck (NC) were obtained, and muscle strength assessments (handgrip) were performed by a trained dietitian.

The diagnosis of Metabolic Syndrome (MS) was performed according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). If three of five following criteria was positive in a patient; higher blood pressure than 135/85 mmHg, having abdominal obesity (>102 cm WC for males, >88 cm WC for females), higher triglyceride levels than 150 mg/dl, lower HDL levels than 40 mg/dl (50 mg/dl for females) and higher fasting glucose levels than 110 mg/dl, we decided he/she had metabolic syndrome (34).

Statistical Analyses

Statistical analyses were performed using SPSS software version 23. The variables were investigated using visual (histogram) and analytical methods (Kolmogorov-

Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations (mean ± SD). When evaluating general characteristics of the patients, Student's t-test was used to compare means of normally distributed variables and Mann-Whitney-U test was used to compare the means of non-normally distributed variables between male and female patients. The Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), were used to compare the proportions of different stages of disease activities in male and female patients. Also for the comparison of BMI classification of male and female patients, Chi-square test was used. The correlations between disease activity parameters, adiponectin levels and body composition variables were calculated using Pearson test, if both of the test parameters were normally distributed. For non-normally distributed variables, Spearman test was used. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Fifty-five RA patients (80% female, 20% male) with a mean disease duration of 127.0 ± 120.6 months were included to the study. The mean age of the study group was 53.5 ± 9.7 years. The general characteristics of study group and comparisons according to males and females are summarized in **Table 1.** Mean serum adiponectin value was 16.08±6.95 μg/mL and did not differ significantly with gender. Adiponectin was positively correlated with body fat (%) (r=0.427, p=0.001) and FMI (p=0.031; r=0.296), and negatively correlated with fat-free mass (%) (r=-0.316, p=0.021) as can be expected. However, no significant correlations were found between adiponectin levels and parameters such as age (p=0.123), disease duration (p=0.432) number of comorbidities (p=0.203), DAS-28-ESR score (0.728), DAS-28-CRP score (0.359), HAQ score (p=0.706), and RA-QoL score (p=0.730). **(Table 2).**
Furthermore, there were also no significant correlations between serum adiponectin levels and anthropometric measurements (weight, WC, MUAC, NC, CC) or handgrip strength. Corticosteroid use was significantly more prevalent among female patients (p=0.037).

According to DAS28-ESR parameters, among 55 patients, 21 were in remission period, 10 were in low disease activity, 22 were in moderate disease activity, and 2 were in severe disease activity periods. There were no statistically significant differences between these groups in terms of weight (p=0.874), waist circumference (p=0.877), MUAC (p=0.844), neck circumference (p=0.265), handgrip strength (p=0.880), and body fat (p= 0.824).

According to BMI scores, out of 55 patients, 8 were within normal range, 13 were overweight, and 32 were obese. There were no statistically significant differences between BMI groups in terms of adiponectin (p=0.207), DAS-28-ESR score (p=0.255), disease duration (p=0.367), HAQ (p=0.148), and RA-QoL (p=0.152).

Table 1 General characteristics of RA patients according to gender (n = 55)

Characteristics	Men (N=11)	Women (N=44)	P value	Total
Sex	11 (20.0)	44 (80.0)	-	55 (100.0)
Age (y)	53.8 ± 10.9	53.5 ±9.5	0.924	53.5 ± 9.7
Duration of RA (m)	155.9 ± 169.2	119.8 ± 106.5	0.776	127.0 ± 120.6
Co-morbidity (+)	7 (63.6)	29 (65.9)	1.000	36 (65.5)
Medication				
Synthetic DMARD	9 (81.8)	40 (90.9)	0.059	49 (89.1)
Biological DMARD	1 (9.1)	-		1 (1.8)
Synthetic & Biological DMARD	1 (9.1)	-		1 (1.8)
Corticosteroid use	1 (9.1)	20 (45.5)	**0.037***	21 (38.2)
NSAI	3 (27.3)	20 (45.5)	0.326	23 (41.8)
DAS28ESR	2.92 ± 1.5	3.1 ± 1.0	0.501	3.1 ± 1.1
DAS28CRP	2.3 ±1.5	2.1 ± 0.9	0.792	2.1 ± 1.0
HAQ	0.6 ±0.6	1.2 ± 1.2	**0.026***	1.1 ± 1.2
RA-QoL	6.0±4.5	12.7 ± 8.3	**0.012***	11.4 ± 8.1
BMI (kg/m2)	26.5 ±3.7	32.5 ±5.3	**0.001***	31.3 ± 5.5
FMI (kg/m2)	7.7 ± 2.8	13.0 ± 3.4	**0.000***	11.9 ± 3.9
FFMI (kg/m2)	18.9±1.1	19.2 ± 2.1	0.556	19.2 ± 1.9
CRP (mg/L)	1.8 ± 2.5	1.0 ± 0.9	0.542	1.13 ± 1.39
Adiponectin **(μg/mL)**	13.2 ± 4.3	16.7 ± 7.3	0.158	16.08 ± 6.95
Sedimentation	24.5 ± 25.2	24.8 ±20.8	0.760	24.69 ± 21.51

*__Mann-Whitney U__ test was used.
HAQ: Health Assessment Questionnaire
RA-QoL: Rheumatoid Arthritis Patients Quality of Life
BMI: Body Mass İndex
FMI: Fat Mass İndex
FFMI: Fat Free Mass İndex

According to DAS28-CRP parameters 72.7% of patients were in remission state, 14.5% had low 10.9% had moderate, and 1.8% had severe disease activity. Although disease activity parameters did not differ among female and male patients, females had significantly higher HAQ (functional status) and RA-QoL (quality of life) scores compared to males (1.2±1.2 vs. 0.6±0.6, p<0.05 and 12.7±8.3 vs. 6.0±4.5, p<0.05; respectively) **(Table 2).**

Table 2. The correlations between diseases variables and body composition

	BMI (kg/m2)		**Body Fat (%)**		Body Fat (kg)		Fat-free mass (%)		**Fat-free mass (kg)**		**FFMI (kg/m2)**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	**0.310**	**0.021**	0.392	0,003	0.305	0.024	-0,373	0,005	-0.072	0.599	0.182	0.183
Disease duration	-0.002	0.990	-0.115	0.405	-0.112	0.417	0.013	0.927	-0.203	0.137	-0.070	0.614
DAS28-ESR	-0.004	0.979	0,073	0,597	0.068	0.622	0,008	0,954	0.017	0.902	-0.010	0.942
DAS28-CRP	-0.075	0.587	-0,058	0,676	-0.069	0.618	0,130	0,345	-0.012	0.931	-0.059	0.668
HAQ	0.198	0.147	0,236	0,083	0.192	0.160	-0,191	0,162	-0.204	0.135	0.070	0.612
RA-QoL	0.173	0.207	0,129	0,349	0.089	0.517	-0,194	0,156	-0.309	0.022	-0.041	0.768
Number of comorbidities	0.112	0.415	0.246	0.070	0.195	0.153	-0.115	0.405	0.016	0.906	0.135	0.327
Adiponectin	0.178	0.201	**0.427**	**0.001**	0.234	0.092	-0.316	0.021	-0.131	0.348	0.021	0.883

Disease duration was significantly shorter in patients with metabolic syndrome, but there is no relation between age, Das28-esr, Das28-crp, Haq, RaQol and metabolic syndrome **(Table 3).**

Table 3. Relationship between disease parameters and metabolic syndrome

Variables	**Metabolic Syndrome (+)**	**Metabolic Syndrome (-)**	**P value**
Disease parameters			
Age (y)	55.9±9.3	51.9±9.7	0.137
Duration of disease (m)	94.8±101.0	148.4±129.1	**0.028**
DAS28-ESR	3.2±1.1	3.0±1.0	0.334
DAS28-CRP	2.3±1.3	2.0±0.8	0.724
HAQ	1.0±0.6	1.1±1.5	0.559
RAQOL	11.9±8.2	11.0±8.2	0.724

DISCUSSION

In the current study, adiponectin levels were found to correlate with body fat (%), FMI, and fat-free mass. There is no correlation between disease activity parameters and adiponectin levels.

WHO guidelines report that 48% of RA patients have normal BMI, 20% are overweight and 32% are classified as obese (15). In our study, the mean BMI of patients was 31.3±5.5, which puts the group into the obese classification. Additionally, the mean BMI of the female group was significantly higher than that of the male group. Obesity rate in RA patients was reported as 31% and 40.3% in two studies (16, 17). A study by Younis and colleagues found obesity rate as 46.6% in RA patients and reported higher DAS28 results in overweight patients, suggesting a positive relationship between obesity and disease activity (18). In this study, obesity rate according to BMI was found as 58.1% which is high when compared to the literature. It was not correlated with disease activity. This might be due to differences in social and cultural characteristics, physical activity, and eating habits. We found no relationships between BMI values and DAS28, adiponectin levels, disease duration, HAQ, RA-QoL, and sedimentation. This can be due to the factor that a majority of our patients were in remission or low disease state.

Body mass index (BMI), is used to assess obesity at a body-wide perspective. In BMI calculation, body weight is directly used without considering the percentage of tissues that comprise it. The percentage of fat mass and fat-free mass has been shown to vary between individuals (19). Therefore, in order to better determine body composition and its effects, we evaluated fat mass (FM) and fat-free mass (FFM) in our study. Furthermore, we performed anthropometric measurements, including circumferences of the waist (WC), mid-upper arm (MUAC), calf (CC) and neck (NC) in addition to muscle strength (handgrip) assessment. We found FM to be significantly higher in females, while there was no difference between genders in terms of FFM. Body fat had a significant positive correlation with age and adiponectin. However, parameters such as disease duration, DAS28-ESR, DAS28-CRP, HAQ, RA-QoL and number of comorbidities were not correlated with body fat. There was a significant negative correlation between FFM and RA-QoL. As can be expected, adiponectin was positively correlated with body fat and inversely correlated with FFM%. In another study from Turkey, females with RA were found to have low grip strength and lean body mass (20). Book et al. reported that, in early RA, both males and females had lower mean mass compared to controls. However, when females were assessed separately, they were found to have higher BMI,

FM, and fat/mass ratio compared to controls. Although total body fat mass (BFM) values were higher, their correlation with disease severity and activity markers were low, only DAS28 was significantly associated with BFM and this was true only in females (21). The lack of significant associations may be explained by the high number of patients in remission and low disease activity. Although the relationship between obesity and RA disease is yet be fully understood, some studies showed direct associations between BMI and disease state (22). It is important to keep in mind that, in advanced RA, loss of normal body composition (i.e. being underweight or overweight) is associated with increased severity of the disease. Active/severe disease causes weight loss, and controlled disease may lead to weight gain (23). Weight gain increases intra-abdominal and visceral fat, which may cause metabolic syndrome due to development of hyperinsulinemia, insulin resistance, glucose intolerance, lipid abnormalities, inflammation and endothelial dysfunction (5, 24).

In our study, patients who were diagnosed with metabolic syndrome had higher BMI, FM and FFM values. However, surprisingly, the duration of disease was shorter in patients with metabolic syndrome. This may be explained by numerous factors including disease state and control, genetic predisposition, patient physical activity and life-style. Whatever the explanation, this finding warrants and requires further research before any conclusion can be drawn.

Adiponectin is one of the pro-inflammatory cytokines produced by adipose tissue (25). Thus, adipose tissue and adiponectin may have an important role in the pathophysiology of inflammatory disorders. We found that adiponectin levels were positively correlated with body fat (%) and negatively correlated with fat-free mass (%). However, no correlations were found for anthropometric measurements or handgrip strength. Furthermore, no correlations were found between adiponectin levels and disease variables such as age, disease duration, number of comorbidities, DAS28-ESR score, DAS28-CRP score, HAQ score and RA-QoL score. On the other hand, adiponectin levels were positively correlated with FMI score. In one study, a significant inverse correlation was found between adiponectin and waist circumference (26). Likewise, Baker et al. (27) have reported negative correlation between BMI and adiponectin which is agreement with the findings of Oranskiy et al. (28) who reported that adiponectin was reduced in persons with low or normal BMI, and increased in overweight and obese subjects. In a study comparing RA patients and controls by Chen et al., adiponectin levels were found to be increased in RA, and the DAS28 and ESR scores were positively correlated with these increased levels (12). However, Senolt and colleagues found no correlations between age, disease duration, BMI, and disease activity, similar to our study. In another study, there were also no correlations between adiponectin levels and DAS28-ESR and HAQ scores (29). Furthermore, a meta-analysis study also reported that there was no association between disease activity (determined via DAS28 and CRP) and adiponectin levels in RA (30).

As can be seen, there are various results and conclusions in terms of adiponectin level and its effects on RA. A broad range of factors may have caused these results, including comorbidities, body composition, and life-style and cultural differences. However, one particular cause could be that only some isoforms of adiponectin may influence inflammation; thus, measurement of total adiponectin may be misleading (31).

The cross-sectional nature of the study and the absence of a control group may be considered as limitations. However, the inclusion of anthropometric measurements and determination of body composition in addition to previously investigated parameters and number of study group are strengths of our study.

In the current study, adiponectin levels were found to be positively correlated with body fat (%) and negatively correlated with fat-free mass (%). The RA-QoL score was also negatively correlated with fat-free mass. A nother important finding was the shorter disease duration in patients with metabolic syndrome which requires additional studies in order to be explained thoroughly. However, no relationships were found between adiponectin levels and disease activity parameters or body composition measurements. Multifactorial pathogenesis between adiponectin isoform measurements and disease activity status should be considered in the evaluation of adiponectin and related parameters.Future studies comprising patients with different disease activity may explain conflicting results.

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