Which Factors are Predictive for Presence of Insulin Resistance in Patients with Rheumatoid Arthritis?
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ABSTRACT

Aims: The aim of this study was to investigate of obesity and insulin resistance and associated factors in patients with rheumatoid arthritis (RA).

Methods: We included a cohort of patients with RA. In the clinical research, duration of disease, existence of clinical remission (Disease activity index (DAS) 28 below 2.6), amount of the relevant disease-modifying antirheumatic drugs were derived from clinical datum. Cumulative corticosteroid dose was calculated by duration of corticosteroid usage and ratio of physiologic dose. Insulin resistance was calculated with homeostasis model of assessment of insulin resistance.

Results: A total of 64 patients aged between 22–77 with RA were studied. Insulin resistance were detected in 34.4 % (n= 22) of patients. There was a statistically significant correlation between body mass index and DAS28 scores ($r= 0.469, p= 0.000$). We found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year ($p= 0.001$). As long as, we did not detect insulin resistance none of the patients (n= 7) treated with TNF blockers. Cumulative steroid dose, presence of obesity and DAS28 were the best predictors for insulin resistance according to multivariate linear regression analysis ($R^2c=0.242, F=6.39, p<0.001$). In this model $R^2c$ for cumulative steroid dose was 0.113 ($F= 7.88 p<0.007$) and obesity was 0.147 ($F= 10.67, p=0.02$).

Conclusions: Obesity and longstanding corticosteroid use were determinants of insulin resistance in patients with RA. Medications such as methotrexate, TNF blockers may help to reduce insulin resistance.

Key words: Insulin resistance, methotrexate, obesity, rheumatoid arthritis remission

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease associated with increased disability, morbidity and mortality (1). The synovial membrane is the primary site of rheumatoid inflammation. In addition to articular symptoms, extraarticular manifestations are present approximately in %30 of chronic patients with RA. Systemic inflammation can lead to constitutional symptoms such as low grade fever, fatigue, malaise, myalgias, weight loss and metabolic disorders.

In the last two decades adipose tissue was promoted to an active endocrine organ and was also implicated in obesity which is a low-grade inflammatory state, such as inflammatory conditions including RA (2).

High levels of leptin, adiponectin and resistin in adipose tissue are associated to increased inflammatory state in obesity. As well as increased insulin resistance and metabolic demand of insulin are considered another problem related to obesity. Some researchers claim that there may be a possible aetiological link between obesity and certain autoimmune diseases such as RA (3,4).

The relationship between obesity and inflammation has been demonstrated in the past decades and those two entities are certainly linked with insulin resistance. Obesity studies in patients with endocrinologic diseases and other conditions related to insulin resistance have pointed tumour necrosis factor (TNF), interleukin IL-6 and IL-8 levels (5,6). The mechanisms generating low level inflammation in obesity are not known in depth. Although patients with RA show a high prevalence of obesity, dyslipidemia or impaired glucose metabolism, few studies have specifically investigated insulin resistance in RA. This study was accomplished for assessment of obesity and insulin resistance and associated factors in patients with RA.
MATERIAL AND METHODS

64 enrolled patients who were followed at the Rheumatology Polyclinics in the Medicine Faculty Hospital between April 2013 and April 2014 and fulfilled the ACR/EULAR 2010 RA classification criteria, were included in the study. ACR/EULAR RA classification criteria included a) Joint involvement b) RF and Anti-CCP positivity c) Acut phase reactants d) Duration of symptoms (7).

Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Sakarya University. The patients’ age, gender, body mass index (BMI) were registered. In the clinical research, the patients’ duration of disease, the existence of clinical remission, the relevant disease-modifying antirheumatic drugs (DMARD) amount, the existence of family history were taken as notes. Cumulative corticosteroid dose was calculated by duration of corticosteroid usage and ratio of physiologic dose. BMI values < 18.5 kg/m² are considered underweight, between 18.5-24.9 as normal, 25-29.9 as overweight and values greater than 30 indicated obesity (8). Thirty two patients with BMI higher than 30 kg/m² were assigned as obesity group. We excluded patients with diabetes mellitus and acute or chronic pancreatic disorders.

Disease Activity Score (DAS 28) remission criteria, involving C reactive protein (CRP), swollen and tender joint counts and patient’s global health assessment were used to determine whether the disease in remission. A score of DAS28 between 2.6-3.2 indicates low disease activity, 3.2-5.1 moderate and > 5.1 high disease activity (9).

In this study, the assessment of insulin was done with experimental method in which in vitro frozen (-20°C) serum samples were re-evaluated. The following parameters were determined from the patients' own charts: fasting plasma glucose, hemoglobin A1C (HbA1C),
erythrocyte sedimentation rate (ESR), CRP, hemogram parameters such as white blood cell (WBC), platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (N/L ratio), ferritin levels by standard laboratory methods.

Insulin resistance was evaluated from the homeostasis model of assessment of insulin resistance (HOMA-IR) (10). The HOMA-IR was calculated from fasting plasma glucose and fasting serum insulin concentrations using the following formula (fasting plasma glucose [mg/dL] × fasting serum insulin [mU/L]/405) Therefore, values were considered abnormal when HOMA-IR index was >2.5.

**Statistical Analysis**

Descriptive statistics were performed and indicated as mean ± standard deviation and median for continuous variables. All qualitative data are expressed as frequencies and percentages. Correlations were investigated by univariate analysis and multivariate linear regression models, when appropriate. Statistical testing of differences in continuous variables between groups was made by Mann Whitney U test. P values less than 0.05 were considered significant. All statistical analyses were done using SPSS for windows version 20.0 program.

**RESULTS**

We included 64 patients with RA in the study. The clinical characteristics of the patients were given at Table 1.

In obesity group and controls showed homogeneous characteristics in terms of demographical and some clinical characteristics (p >0.05) (Table 2).
The ratio of patients with clinical remission were 37.5 % (n= 24) and low disease activity and moderate disease activity were 20.3 % (n= 13), 42.2 % (n= 27), respectively. In evaluation of disease activity by DAS 28, there was a statistically significant correlation between BMI and DAS 28 scores as shown in Figure 1 \((r= 0.469, p= 0.006)\).

Insulin resistance were detected in 34.4 % (n= 22) of patients. We found differences in some laboratory measurements; N/L ratio was statistically significant lower in obese patients \((p= 0.036)\). HbA1c levels was higher in obese patients \((p= 0.033)\). Insulin resistance was found in obesity group in comparison of controls \((z= -2.089, p= 0.037)\). Furthermore there were no statistically significant differences between laboratory parametres other than HbA1c, N/L ratio, insulin resistance \((p > 0.05)\) (Table 3).

There was no difference between the types of other DMARDs in each group. Methotrexate has been the first choice in both groups. The ratio of medication used in obesity group were as the follows; methotrexate, leflunomid, hydroxychloroquine sulphate, sulphasalazine, TNF blockers (2 patients adalimumab, 1 patient golimumab) and rituximab (1 patient), 75 %, 42 %, 31 %, 24 %, 9 % and 3 %, respectively. The ratio of medication in control group were as the follows; methotrexate, leflunomid, hydroxychloroquine sulphate, sulphasalazine and TNF blockers (2 adalimumab, 2 etanercept), 75%, 59%, 42%, 42% and 12%, respectively.

There was significant correlation between insulin resistance and cumulative corticosteroid dose \((r= 0.336, p= 0.007)\). We found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year \((16 % vs 50, r= -0.428, p= 0.001)\). As long as, we did not detect insulin resistance none of the patients (n= 7) treated with TNF blockers.
A significant correlation between insulin resistance and BMI scores was found \((r = 0.383, \ p = 0.002)\). A moderate correlation was found between insulin resistance and cumulative steroid dose \((r = 0.436, \ p = 0.000)\). A weak correlation was found between insulin resistance and CRP levels \((r = 0.277, \ p = 0.045)\). There was no correlation between insulin resistance and other clinical parameters (age, sex, disease duration, cigarette smoking, family history)\((p > 0.05)\).

To establish the best model to predict insulin resistance multivariable linear regression analysis was performed choosing the variables that were significantly correlated by univariate analysis with insulin resistance. Thus, the dependent variable was the insulin resistance and the independent variables were DAS28, cumulative steroid dose, BMI, respectively. The stepwise procedure selected DAS28, cumulative steroid dose, presence of obesity as the best predictors \(R^2c = 0.242, \ F = 6.39, \ p < 0.001\). In this model \(R^2c\) for cumulative steroid dose was 0.113 \((F = 7.88, \ p < 0.007)\) and obesity was 0.147 \((F = 10.67, \ p = 0.02)\). When we added HbA1c and N/L ratio to the model, these parameters have been established not a significant predictor of insulin resistance \(R^2c = 0.031, \ F = 0.901, \ p = 0.412\).

**DISCUSSION**

Obesity and inflammation are clearly related to insulin resistance and evidence of this relationship has been revealed in the last decades. The most important theory is the local cellular hypoxia of adipose tissue and activation of inflammatory cytokines secreted by adipocytes such as resistin, adiponectin and leptin (11). Insulin resistance is a pathological condition characterised by defective insulin signal processing and alteration of the physiological response of peripheral tissues to insulin hormone. It might be inevitable that
the high levels of proinflammatory cytokines that release in chronic diseases such as RA, would induce an inappropriate tissue response to insulin. Alongside the present studies with conflicting results about insulin resistance in RA, there are no conclusive studies about medications’ effects on insulin resistance. The pathogenesis of this condition is not clearly known, but it is needed to perform more detailed researchs.

Ajeganova et al (12). showed that high BMI scores were poor prognostic markers for patient with RA. In recent years it has been suggested that adiponectin which is secreted from adipose tissue, is associated with disease progression in RA (13, 14, 15). This molecule may induce osteoclast differentitation by stimulating receptor activator of nuclear factor kappa-B ligand (RANKL), and also may upregulate vascular endotelial growth factor (16). In a clinical research, Harle et al (17) conclued that adalimumab therapy did not induce decrease in adiponectin and leptin levels. Although presence of these studies, there are some controversal data about adiponectin and leptin in RA. Towards the results of our study, receiving regular treatment at least 1 year, it may be generally provided that disease activity of patients with RA was higher in obes patients than controls. To our knowledge, adipose tissue may blockade remission by inducing the production of cytokines such as TNF alpha, IL1 ve IL6.

In the literature, vast majority of studies about insulin resistance are related to determine cardiovascular risk in patients with RA. Chung et al (18) studied insulin resistance in 104 patients with RA and compared the results with those of 124 cases of systemic lupus erythematosus. They found that patients with RA were more likely to develop insulin resistance than lupus patients. Also, this study revealed that BMI score was an independent risk factor unrelated to corticosteroid use. There was no detailed data about calculation of corticosteroid use in above study. Furthermore they found that insulin resistance correlated
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with DAS 28 scores, CRP, ESR, extent of coronary calcification. La Montagna et al (19) determined high correlation between insulin resistance and subclinical atherosclerosis.

We pointed out one of the important details in this study that the current cumulative steroid dose and daily steroid dose were indicated separately. Moreover, in the development of insulin resistance accumulation of steroid dose may be considered to be more effective. Dessein et al (20) studied insulin resistance and beta cell function in 94 patients with RA. They concluded that HOMA-IR was related to marker for inflammation such as CRP, ESR and diseases activity measured by DAS 28. Also, they showed insulin resistance was associated with waist circumference, presence of arterial hypertension and use of diuretics and beta-blockers. Multiple regression analysis indicated that the most significant factor with insulin resistance was abdominal obesity (39%-56%) although disease activity was less (5%). Beta cell function was evaluated with HOMA-%B in this study, cumulative steroid dose was the most important factor of determining beta cell function. Other studies have also pointed a positive relationship between CRP levels and HOMA scores in patients with RA and was attributed an important role of this protein (20, 21).

Contrary to these study, Garcia Diaz (22) found no differences in HOMA index between 74 patients with RA and controls. Insulin resistance was not related to disease activity and inflammatory activity. A correlation was found only between insulin resistance and waist circumference.

The main strength and originality of our study are the identification of risk factors and finding out which treatments affect insulin resistance in patients with RA. In our study, we found that the cumulative steroid dose and obesity were the most important factor affecting insulin resistance. Also we claimed that CRP levels and disease activity were relatively less impact on insulin resistance. According to the multiple regression analysis, we showed that
HbA1c and N / L ratio aren’t valuable. One of the advantage of the study was that cumulative steroid dose was to be well quantified.

RA medications that affect insulin resistance in the literature, especially when compared to the multitude of studies on TNF blockers attract attention. There are conflicting results of those studies on TNF blockers. Whereas few studies resolved that there was no improvement in insulin resistance with TNF blockers (23, 24). The majority of studies concluded that there was a reduction of insulin resistance in patients receiving TNF blockers for RA (25,26). Only 7 patients using TNF blockers were included in the study and insulin resistance was not observed in anyone.

Neutralisation of TNF by TNF blockers can decrease cytokines which stimulates the development of insulin resistance. Furthermore, we found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year (16 % vs %50, r= -0.428, p= 0.001).

In light of our study, corticosteroids and obesity can be seen substantially responsible for insulin resistance in these patients. We also evaluated the remarkable effect of methotrexate for elimination of insulin resistance. They are relatively novel findings for patients with RA. It is noteworthy that usage of methotrexate and TNF blocker can prevent the development of insulin resistance.

As a contradiction, low-dose continuous corticosteroid use have suggested as DMARDs in RA (27) This condition will create a confusing situation for clinicians. These data suggest that their effects of insulin resistance and impaired glucose metabolism counteracts their beneficial effect on inflammation. In the light of this information, we may recommend to clinicians that short-term use of corticosteroids because of side effects on
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glucose metabolism and burden of disease more than conventional DMARDs and TNF-blocker.

**CONCLUSION**

Obesity and longstanding corticosteroid use were determinants of insulin resistance in these patients. Also, higher BMI was associated increased disease activity of RA. Steroids can inhibit the activity of the disease otherwise it can lead to metabolic problems. We can emphasise that in RA treatment, approach that are more physiologically should be use more MTX and TNF blockers, less steroids.
REFERENCES


9. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-


Table 1: Clinical characteristics of 64 study patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD years, IQR</td>
<td>56.23 ± 11.26 [56.50]</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>76.6</td>
</tr>
<tr>
<td>Cigarette smoking, % patients</td>
<td>32.8</td>
</tr>
<tr>
<td>BMI, kg/cm², IQR</td>
<td>29.41 ± 5.26 [28.62]</td>
</tr>
<tr>
<td>Disease duration, mean ± SD years, IQR</td>
<td>7.76 ± 7.92 [6.50]</td>
</tr>
<tr>
<td>Rheumatoid arthritis family history, % patients</td>
<td>46.8</td>
</tr>
</tbody>
</table>

*BMI: Body mass index

Table 2: A comparison of rheumatological features in RA patients with or without obesity

<table>
<thead>
<tr>
<th>Feature</th>
<th>Obesity group (n=32)</th>
<th>Control group (n=32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD years</td>
<td>56.41 ± 9.38</td>
<td>56.06 ± 13.03</td>
<td>0.941</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>77.5</td>
<td>75.2</td>
<td>0.615</td>
</tr>
<tr>
<td>BMI, kg/cm²</td>
<td>33.65 ± 3.67</td>
<td>25.17 ± 2.37</td>
<td>0.690</td>
</tr>
<tr>
<td>Cigarette smoking, % patients</td>
<td>32.9</td>
<td>32.1</td>
<td>0.400</td>
</tr>
<tr>
<td>Disease duration, mean ± SD years</td>
<td>7.87 ± 7.72</td>
<td>8.06 ± 7.85</td>
<td>0.902</td>
</tr>
<tr>
<td>Rheumatoid arthritis family history, % patients</td>
<td>37.5</td>
<td>40.6</td>
<td>0.799</td>
</tr>
</tbody>
</table>

*BMI: Body mass index
Table 3: Comparison of laboratory characteristics in patients and control group

<table>
<thead>
<tr>
<th></th>
<th>Obesity group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>101.44 ± 16.04</td>
<td>94.25 ± 12.05</td>
<td>0.098</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.61 ± 0.54</td>
<td>5.24 ± 0.70</td>
<td><strong>0.033</strong></td>
</tr>
<tr>
<td>C reactive protein</td>
<td>6.70 ± 3.58</td>
<td>6.53 ± 6.73</td>
<td>0.113</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>17.91 ± 14.83</td>
<td>19.10 ± 14.01</td>
<td>0.276</td>
</tr>
<tr>
<td>Platet count</td>
<td>242.91 ± 57.58</td>
<td>240.69 ± 56.95</td>
<td>0.629</td>
</tr>
<tr>
<td>Mean platelet volume</td>
<td>7.65 ± 0.83</td>
<td>7.35 ± 0.91</td>
<td>0.086</td>
</tr>
<tr>
<td>Neutrophil/lymphocyte</td>
<td>2.08 ± 0.77</td>
<td>2.81 ± 1.38</td>
<td><strong>0.036</strong></td>
</tr>
<tr>
<td>Ferritin</td>
<td>45.07 ± 54.63</td>
<td>67.46 ± 81.21</td>
<td>0.486</td>
</tr>
<tr>
<td>Insulin</td>
<td>10.57 ± 9.64</td>
<td>9.56 ± 4.46</td>
<td>0.224</td>
</tr>
<tr>
<td>Insulin resistance (% patients)</td>
<td>46.9</td>
<td>21.13</td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>

*HbA1c: Glycated hemoglobin
Figure: Correlation between body mass index and disease activity in patients with rheumatoid arthritis