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Research Article

# Endothelial Function, Insulin Resistance, Serum Adiponectin Level in Rheumatoid Arthritis Females with Renal Dysfunction and Its Dynamics with L-Arginine Aspartate Supplementation

**Olexandr Kuryata and Oksana Sirenko***

## Abstract

**Purpose:** To evaluate endothelial function, insulin resistance, serum adiponectin level in rheumatoid arthritis females with renal dysfunction and its dynamics with the L-Arginine aspartate supplementation

**Materials and methods:** 69 females with rheumatoid arthritis (RA) and renal dysfunction were enrolled. Patients were divided into group received L-Arginine aspartate and placebo group. Serum insulin, adiponectin were measured at the baseline and after 4 weeks. The level of insulin resistance, GFR was calculated. Determination of flow mediated vasodilation was performed at the baseline and after 4 weeks.

**Results:** EDVD was significantly lower among the RA females with renal dysfunction ($p<0.05$), serum adiponectin, IR level - significantly higher ($p<0.05$). It was estimated increased mean EDVD by 24.5% ($p<0.001$) with L-Arginine treatment. The level of insulin to the end of the study was lower on 20.3 % ($p=0.002$), insulin resistance – on 11.9 % ($p=0.001$) matched by HOMA1-IR and on 29.4 % ($p=0.002$) - by HOMA2-IR among patients received L-Arginine aspartate. The level GFR to the end of the study increased by 11.9 % ($p=0.02$).

**Conclusions:** Females with rheumatoid arthritis and renal dysfunction are characterized by high frequency endothelial dysfunction, adiponectin level changes, insulin resistance. Endothelial dysfunction correction in RA females with renal dysfunction with L-Arginine aspartate may cause benefit effects on range of cardio-metabolic factors.

**Keywords**

Rheumatoid arthritis; Renal dysfunction; Endothelial dysfunction; L-Arginine

## Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases in the general population [1]. It has been established that the leading cause of death in RA pts is atherosclerotic cardiovascular diseases, primarily ischemic heart disease [2]. However, there are a number of scientific questions required further studies. Thus, the features of atherosclerotic lesions of arteries in various clinical RA variants, the influence of risk factors, comorbid diseases and antirheumatic drugs on a therogenesis are not completely studied [3-5].

An unfavorable prognosis in patients with RA can be associated with kidney damage [6]. The incidence of kidney damage in RA, according to different authors, is from 57 to 73% [7,8]. The formation of nephropathy in RA has complex multifactor character and manifests itself in various clinical and morphological variants [9]. The development of chronic kidney disease (CKD) in RA can be associated with cardiovascular pathology, while renal pathology itself is a risk factor for cardiovascular disease [10]. At the same time, large-scale epidemiological studies on the prevalence of CKD in RA and associated risk factors have not been carried out, and the available data are contradictory [11].

Evaluation of cardiovascular risk using existing scales for RA pts is not effective enough [12]. In this way relevant to search for biomarkers of subclinical atherosclerosis in these patients to improve the assessment of cardiovascular risk and early prevention. Thus, in previous works we showed increased frequency of endothelial dysfunction, insulin resistance (IR), adiponectin level in hypertensive RA females associated with carotid atherosclerosis [13]. Its seems that the mechanisms of development of endothelial dysfunction, insulin resistance IR, disorders of adipose tissue metabolism in RA females with comorbid pathology are complex, therefore their further research and correction methods are relevant. There is also evidence that the use of L-arginine aspartate for 4 weeks in the combined therapy in hypertensive RA females allows to improve vascular endothelial function, reduce insulin resistance, and contribute to adiponectin level normalization [13,14-21]. It's promising in our opinion also to study these cardiometabolic factors and their correction in RA females taking into account the function of the kidneys.

**We aimed** to evaluate endothelial function, insulin resistance, serum adiponectin level in rheumatoid arthritis females with renal dysfunction and its dynamics with the L-Arginine aspartate supplementation.

## Patients and Methods

### Patients

The present study was conducted with approval from the Ethics Committee at State Establishment «Dnipropetrovsk Medical Academy of Health Ministry of Ukraine» according to the principles outlined in the Helsinki declaration.

All participants of research gave informed, written consent. 69 females from 45 to 65 years with established diagnosis of RA according to the 2010 American College of Rheumatology/EULAR criteria for RA and renal dysfunction defined as an estimated glomerular filtration rate (GFR)<90 mL/min/1.73 $m^2$ and/or positive proteinuria

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test were enrolled. Only female pts were selected considering the RA gender structure. All patients received stable therapy of RA more than 6 months. Patients with verified diagnosis of ischemic heart disease, diabetes mellitus, CKD with estimated GFR<60 mL/min/1.73 $m^2$ and/or positive proteinuria test for ≥ 3 months and pts with disease activity of RA DAS28 >3.2 haven't included in the study.

Hypertension was estimated in 29 (42%) RA females with renal dysfunction, the median systolic blood pressure was 128.5 [125.5; 133.7] mm Hg, diastolic - 76.4 [72.5; 79.3] mm Hg. The RA activity index on the DAS28 scale was 2.6 [2.1; 2.9] points, the median BMI - 28,3 [25.7; 32.4] kg/$m^2$, GFR - 91.5 [78; 100.5] mL/min/1.73 $m^2$.

Basic disease-modifying RA treatment received all included patients: methotrexate with the average dose 15 [10; 15] mg per week, the average duration of treatment with methotrexate 59 [50; 84] months. Glucocorticoids received 48 patients (69.6%), the average daily dose of methylprednisolone was 3.8 [2.5; 4.0] mg, the mean duration of glucocorticoid therapy - 42 [30; 51] months. Antihypertensive treatment received all hypertensive RA patients: ACE inhibitors - 21 (72.4%) patients, angiotensin II receptor antagonist – 8 (27.6%), calcium antagonists – 7 (24.0%), b-blockers - 5 (17.2%), diuretics - 10 (34.4%), combination of antihypertensive drugs were treated 13 (44.8%) observed pts. Statins received 20 (28.9%) enrolled patients.

### Assessments

Height, weight, and waist and hip circumference were measured using standard approaches. We assessed disease activity for RA by the Disease Activity Score for 28 joints based on erythrocyte sedimentation rate (DAS28-ESR). C-reactive protein concentrations were determined using immunoturbidimetric methods. Standard laboratory blood tests of erythrocyte sedimentation rate, renal and liver function, hematological parameters, lipids, and glucose were performed. The GFR was estimated using the CKD-EPI formula. Cardiovascular risk was assessed by SCORE models adapted for patients with RA by introducing a 1.5 multiplication factor and total cholesterol/HDL cholesterol ratio according to EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis [15].

Insulin and adiponectin concentrations were measured at the baseline and after 4 weeks using solid-phase sandwich enzyme-linked immunosorbent assays (ELISA) (DRG, Germany and ASSAYPRO, USA respectively). Normal adiponectin concentration in blood serum was considered 3-14 ng/mL, insulin - 2 - 25 μIU/mL. The level of insulin resistance, function of pancreas cells, peripheral tissue sensitivity to insulin index were calculated using the standard formula HOMA1 (E. Bonora, 1998), HOMA2 (Wallace T, 2004) using HOMA 2 Calculator Version 2.2.2. HOMA1-IR values above 2.77 and HOMA2-IR above 1.00 testified insulin resistance.

Determination of flow mediated vasodilation of brachial artery was performed at the baseline and after 4 weeks based on Celermajer's methodic [16]. The diameter of the brachial artery was measured with 7.5 MHz transducer of «Philips Envisor C». Duplex extracranial carotid arteries scaning was performed according to recommendations of the American Society of Echocardiography [17]. Scanning was performed on the unit «Philips Envisor C» in the presence of pulsed color Doppler and Tissue Doppler, using linear sensors 5, 7.5 MHz and 3.5 MHz convex transducer.

Statistical analysis of the data was carried out using licensed software STATISTICA 6.1, SPSS version 22.0 and Microsoft Excel 2013. Due to the distribution of data using non-parametric statistical methods - quantitative characters were presented as median (Me) and interquartile range [25%, 75%]. For comparison of two independent groups of criteria used U-Mann-Whitney and Pearson Square - to compare ratios. For a comparison of all three groups have used multiple comparison of univariate analysis of variance Kruskal-Wallis (Kruskal-Wallis ANOVA). Assessment of the relationship between pairs of independent features, expressed in quantitative value, performed by the coefficient of rank correlation P. Spearman - R. In addition, to determine the independence indices performed uni- and multivariate (binary logistic) regression analysis. To determine the diagnostic efficiency of adiponectin and IR used ROC-analysis, calculating the area under the ROC-curve (AUROC). Statistically significant differences were determined research results at the level of p<0,05.

### Study design

Main group consist of 43 (62.3 %) pts with RA and renal dysfunction (median GFR 74.2 [70.3; 86.2] ml/min/1.73 $m^2$), compare group – 26 (37.7 %) RA pts without renal dysfunction (median GFR 95.8 [88.6; 102.1] ml/min/1.73 $m^2$). In the endpoint patients with renal dysfunction were prospectively randomly and blindly divided into study group patients received L-Arginine aspartate in an oral solution 30 ml/day during 4 weeks in addition to standard treatment (1st group, n=22), and pts received placebo (2nd group, n=21).

## Results and Discussion

The median cardiovascular risk level matched by mSCORE in RA females with renal dysfunction was 4.4 [2.3; 5.2] %, in pts with normal renal function - 3.9 [2.2; 4.8] % (p>0.05). The majority of main group pts had moderate risk level – 23 (53.5 %) pts, the number of low and high risk level pts - 14 (32.6 %), 6 (14%) respectively, there was no significant differences in cardiovascular risk structure compare with compare group (p>0.05). At the same time carotid atherosclerosis has been estimated in 35 (81.4 %) RA females with renal dysfunction and in 14 (53.8%) compare group pts (p<0.05). Among main group pts with estimated carotid atherosclerosis was significantly higher prevalence of atherosclerotic plaques (AP) (Figure 1). The higher incidence of AP in RA patients with renal dysfunction also remained statistically significant with regard to the number of traditional cardiovascular risk factors. RA females with renal dysfunction and carotid atherosclerosis had not significantly higher cardiovascular risk level; it was interpreted in 57.1 % pts as moderate risk level (Figure 2).

The established discrepancy of cardiovascular risk level and subclinical atherosclerosis manifestations may be associated with additional factors. Thus endothelial dysfunction was estimated in the majority of observed pts – 54 (78.3 %). EDVD was significantly lower among the RA females with renal dysfunction – median level 3.5 [2.0; 5.3] %, in pts with normal renal function - 5.9 [4.2; 10.5] % (p<0.05). Significant correlation have been established between EDVD level and of GFR (R=0.72, p<0.05), SCORE level (R=-0,65, p<0.001), diastolic blood pressure (R=-0.58, p<0.05).

Median serum adiponectin level in RA females was 13.2 [11.7; 14.7] mg/ml and significantly higher in RA patients with renal dysfunction (Figure 3) (p<0,05). The results of regression analysis showed factors associated with increased adiponectin level were IR (OR=1.36, p=0.02, 95% CI 1.19-2.1), GFR <90 ml/min/1.73 $m^2$

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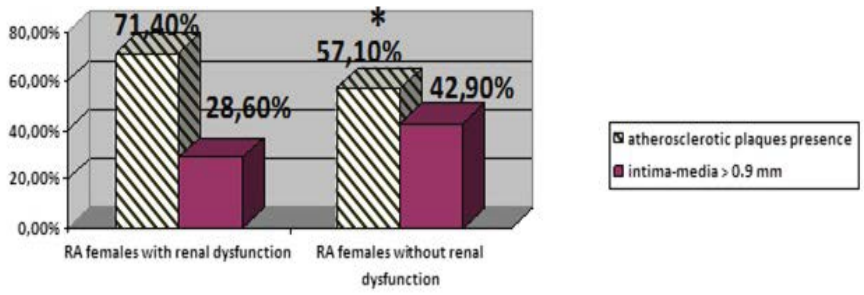


* - significant differences between groups p <0.05 (by Mann-Whitney test)

The structure of estimated subclinical atherosclerosis in RA females

**Figure 1:** The structure of estimated subclinical atherosclerosis in RA females.

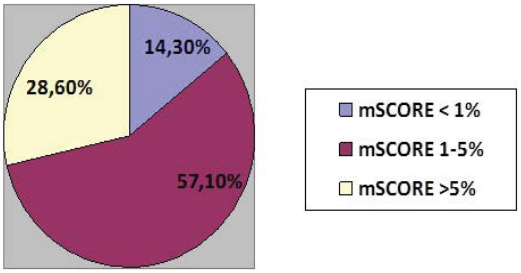


**Figure 2:** The structure of cardiovascular risk level in RA females with renal dysfunction and estimated subclinical atherosclerosis.

(OR=2.11, p=0.003, 95 % CI 1.56-2.12), endothelial dysfunction (OR=2.21, p=0.001, 95 % CI 1.56-2.54), glucocorticosteroid therapy (OR=1.54, p=0.001, 95% CI 1,02-1.87). IR was estimated in 41 (59.4 %) and 55 (79.7 %) of RA females matched by HOMA1-IR and HOMA2-IR respectively, the median level was 3.4 [2.8; 5.7] and 2.2 [1.8; 3.3] respectively. RA females with renal dysfunction were characterized by significantly higher IR level (Figure 4). HOMA2-IR level was correlated with waist circumference (R=0.43, p<0.05), GFR (R=- 0.42, p<0.05), EDVD (R=-0.54, p<0.05), GFR (R=-0.34, p<0.05). According to our data use of the model HOMA2-IR, perhaps more fully reflects the presence of insulin resistance and its association in females with RA.

The results of ROC-analysis stated good quality diagnostic model - AUROC for adiponectin was 0.797 (95% CI 0,602-0,951, p<0.05) and 0.757 (95% CI 0,596-0.876, p<0.05) for the HOMA2 index. After 4 weeks of treatment with L-Arginine it was estimated increased mean EDVD by 24.5% (p<0.001), in compare with standard therapy – on 7.8% (p=0.41). Endothelial function normalizing was achieved in 28 (65.1%) of L-Arginine pts group, that significantly higher than in standard therapy group – in 5 (16.1 %) (p<0.001). EDVD was significantly higher in 1st group pts in compare with standard therapy group to the end of study term (p<0.001) (Table 1).

The level of insulin to the end of the study was lower on 20.3 % (p=0.002), insulin resistance – on 11.9% (p=0.001) matched by HOMA1-IR and on 29.4 % (p=0.002) matched by HOMA2-IR among patients received L-Arginine aspartate. The IR correction was mainly due to increase insulin receptors sensitivity, as evidenced by the dynamics of HOMA2-%B, HOMA2-%S – -8.5% (p=0,002) and +14.4% (p<0.001) respectively (Table 1). The level GFR to the end of the study increased by 11.9% (p=0.02). In the standard treatment group these parameters in the dynamics weren't differ significantly.

The inclusion of L-arginine aspartate contributed to the most significant increase HOMA2-%S on reaching endothelial function correction – on 42.5% compare to patients with EDVD<10% (Table 2). In patients with endothelial dysfunction correction observed a significant decrease of adiponectin in compare to preserved endothelial dysfunction patients on 15.3 % (p=0.01) and GFR increasing on 18.2% (p=0.001). Thus, in RA females observed increased frequency of carotid atherosclerosis, including AP presence with instability signs. However, the majority of this pts had established renal dysfunction and moderate cardiovascular risk level. These study results support the need for RA specific cardiovascular risk stratification models with the consideration of renal function, potentially, the use of novel CVD risk biomarkers. The study results reinforce the need for more awareness in daily clinical practice of increased cardiovascular risk in RA females with renal dysfunction.

It should be noted associative link between the carotid atherosclerosis presence with increased levels of adiponectin in RA females with renal dysfunction differs from the data obtained for the general population [18]. The similar results were obtained Dessein et al. isolated in patients with RA [19] and CKD pts [20]. Perhaps this indicates a non-linear relationship between atherosclerotic vascular lesions and circulating levels of adiponectin in these conditions that requires further detailed study. IR presence, endothelial dysfunction were associated with increased adiponectin level that indicating a complex relationship between muscle and adipose tissue exchange

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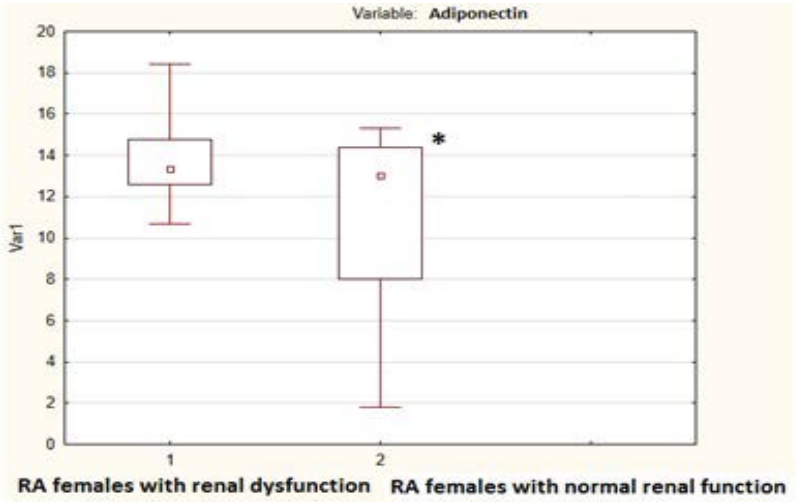


**Figure 3:** Adiponectin level in RA females depending on renal dysfunction.

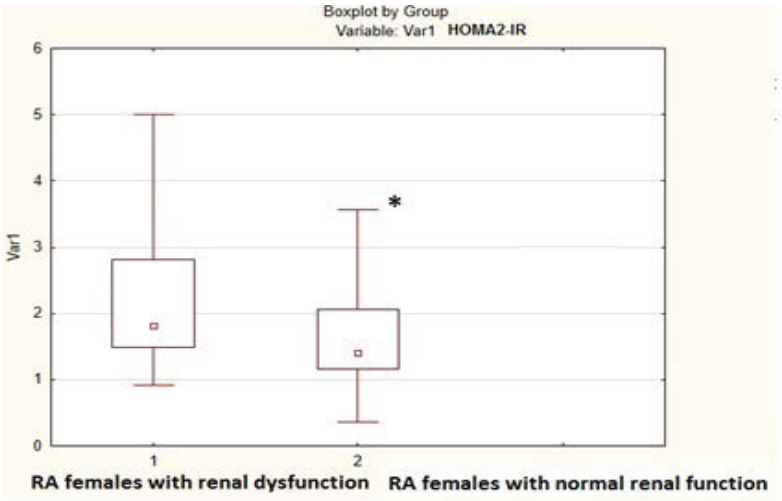


**Figure 4:** HOMA2-IR level in RA females depending on renal dysfunction.

**Table 1:** Dynamics endothelium dependent vasodilatation (EDVD), adiponectin, insulin, insulin resistance levels, GFR after 4 weeks in RA females with renal dysfunction.

| Cardiometabolic risk factors | +L-Arginine aspartate (n=22) | | -L-Arginine aspartate (n=21) | |
|---|---|---|---|---|
| | Baseline | After 4 weeks | Baseline | After 4 weeks |
| EDVD, % | 7,4 [4,6; 7,9] | 9,8 [9,1; 11,3]** | 7,1 [4,7; 8,1] | 7,7 [4,7; 7,5]# |
| EDVD<10% (%) | 63,6 | 31,8** | 66,7 | 71,4# |
| Adiponectin, ng/ml | 12,5 [10,2; 12,3] | 11,4 [9,9; 12,9] | 12,5 [10,4; 13,3] | 11,1 [10,5; 12,4] |
| Insulin, μIU/mL | 12,8 [10,5; 13,6] | 10,2 [9,2; 13,6]* | 12,1 [12,6; 13,3] | 12,4 [11,5; 13,2] |
| HOMA1-IR | 4,2 [3,7; 5,3] | 3,7 [2,7; 4,9]* | 3,8 [2,7; 5,3] | 3,8 [2,5; 5,2] |
| HOMA1-IR>2.77 (%) | 59,0 | 50,0 | 61,9 | 57,1 |
| HOMA2-IR | 1,7 [1,4; 1,9] | 1,2 [1,0; 1,6]* | 1,5 [1,3; 2,1] | 1,3 [1,1; 1,8] |
| HOMA2-IR>1.00 (%) | 63,6 | 45,5* | 61,9 | 57,1 |
| HOMA2-%B | 132,4 [111,7; 135,2] | 121,1 [96,4; 123,4]* | 131,2 [99,4; 138,7] | 127,8 [101,5; 135,7] |
| HOMA2-%S | 60,2 [43,4; 63,4] | 70,3 [37,5; 75,9]* | 61,2 [39,6; 57,5] | 62,3 [42,4; 54,2]# |
| GFR, ml/min/1.73 $m^2$ | 73.8 [70.1; 85.4] | 83.8 [78.5; 91.4]* | 74.1 [71.1; 86.2] | 76.8 [71.1; 85.3] |

**Note:***Significant differences between groups in dynamics p <0.05 (by Wilcoxon test) ** p <0.001 # - Significant differences between the L-Arginine aspartate group and the standard treatment group p <0.05 (by Mann-Whitney test

**Table 2:** The levels of adiponectin, insulin, insulin resistance depending on the degree of endothelial function correction.

| | EDVD after 4 weeks ≥10% | EDVD after 4 weeks <10% | P |
|---|---|---|---|
| Adiponectin, mg/ml | 12,2 [11,4; 13,6] | 14,4 [13,2; 15,5] | **0,01** |
| Insulin, μIU/mL | 9,8 [5,4; 12,4] | 11,3 [8,4; 21,2] | **0,07** |
| HOMA1-IR | 2,4 [2,1; 4,1] | 4,3 [3,9; 5,4] | **0,004** |
| HOMA2-IR | 1,2 [0,9; 1,8] | 2,4 [2,1; 2,8] | **0,002** |
| HOMA2-%B | 134,2 [125,1; 162,3] | 181,8 [147,4; 215,8] | **0,003** |
| HOMA2-%S | 65,4 [42,7; 70,8] | 37,6 [28,4; 42,3] | **0,01** |
| GFR, ml/min/1.73 m2 | 73.4 [68.3; 84.8] | 89.7 [79.6; 94.3] | **0,002** |

**Note:***Significant differences between groups in dynamics p <0.05 (by Wilcoxon test) ** p <0.001 # - Significant differences between the L-Arginine aspartate group and the standard treatment group p <0.05 (by Mann-Whitney test

also needs further study. Present study shows that the endothelial dysfunction correction in RA females with renal dysfunction may cause benefit effects on range of cardio-metabolic factors. Current obtained data may indicate the key role of endothelial function in reducing the sensitivity of peripheral insulin receptors and adiposity dysfunction in RA patients with renal dysfunction, which requires more detailed study. L-Arginine aspartate supplementation seems to be useful tools in the primary prevention in RA patients with renal dysfunction.

## Limitations

However, this study have several limitations. Therefore, only female subjects were chosen for this study. It should be noted that pts had stable therapy of RA more than 6 mounths and low disease activity. The study was carried out in a 4-weeks period and assesses only intermediate end points. However, it cannot be established from the present study whether the changes observed were permanent or reversible. In this regard, more prolonged L-arginine supplimentation study in RA patients with renal dysfunction.

## Conclusions

Females with rheumatoid arthritis and renal dysfunction are characterized by moderate cardiovascular risk level with high frequency of carotid atherosclerosis. Endothelial dysfunction, adiponectin level changes, insulin resistance were estimated in the majority of this patients. Evaluation of serum adiponectin and HOMA2 index could be taken into account in cardiovascular risk assessment in females with rheumatoid arthritis and renal dysfunction.

L-Arginine aspartate supplementation contributes correction of endothelial dysfunction, peripheral insulin resistance, adipose tissue exchange and renal function in females with rheumatoid arthritis.

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