

https://dspace.org/

# Rapid beneficial effect of the IL6 receptor blockade on insulin resistance and insulin sensitivity in nondiastolic patients with rheumatoid arthritis

**N Garcia-Castaneda; S Remuzgo-Martinez; R Lopez-Mejias; F Genre; E et al ...**

https://hdl.handle.net/10539/35085
ISI

Downloaded from a DSpace repository. https://dspace.org/

# Rapid beneficial effect of the IL-6 receptor blockade on insulin resistance and insulin sensitivity in non-diabetic patients with rheumatoid arthritis

S. Castañeda[1], S. Remuzgo-Martínez[2], R. López-Mejías[2], F. Genre[2], J. Calvo-Alén[3], I. Llorente[1], E. Aurrecoechea[4], A.M. Ortiz[1], A. Triguero[1], R. Blanco[2], J. Llorca[5], M.A. González-Gay[2,6,7]

*[1]Rheumatology Division, Hospital Universitario de La Princesa, IIS-Princesa, Universidad Autónoma de Madrid (UAM), Madrid, Spain; [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; [3]Rheumatology Division, Hospital Universitario Txagorritxu, Vitoria, Araba, University of Basque Country, Araba, Spain; [4]Rheumatology Division, Hospital Universitario Sierrallana, Torrelavega, Cantabria, Spain; [5]Division of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, Santander, and CIBER Epidemiología y Salud Pública (CIBERESP), Spain; [6]University of Cantabria, Santander, Spain; [7]University of the Witwatersrand, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, South Africa.*

## Abstract

### Objective

*In patients with rheumatoid arthritis (RA), insulin resistance (IR), a component of the metabolic syndrome, is closely linked to the systemic inflammation induced by proinflammatory cytokines such as tumor necrosis factor-α and interleukin (IL)-6. In the present study, we aimed to assess if an intravenous administration of the anti-IL-6 receptor tocilizumab may yield a rapid improvement of IR in RA.*

### Methods

*50 consecutive non-diabetic patients with RA refractory to methotrexate, undergoing periodic treatment with tocilizumab, were studied. Besides disease activity, serum insulin, insulin/glucose ratio, insulin resistance (HOMA-IR) and insulin sensitivity (QUICKI) indexes were assessed immediately before and 1 hour after the end of an intravenous administration of tocilizumab (given in saline solution over 60 minutes).*

### Results

*When comparing baseline data (immediately before) and 1 hour after finishing tocilizumab administration, we observed a dramatic decrease of the serum insulin levels and insulin/glucose ratio. Also, a statistically significant reduction of IR (HOMA-IR: mean± standard deviation immediately before: 2.62±2.03 vs. 1.65±1.15 1 hour after the end of the infusion ($p<0.01$) and a statistically significant increase of insulin sensitivity (QUICKI immediately before 0.34±0.03 vs. 0.37±0.04 1 hour after the end of tocilizumab infusion ($p<0.01$) was observed.*

### Conclusion

*The intravenous administration of tocilizumab yields a rapid beneficial effect on IR and insulin sensitivity in non-diabetic RA patients. These findings support the potential beneficial effect of the IL-6 blockade on the mechanisms associated with the development of metabolic syndrome and cardiovascular disease in patients with RA.*

**Key words**

rheumatoid arthritis, insulin resistance, insulin sensitivity, HOMA, QUICKI, metabolic syndrome, biologics, anti-IL6 receptor tocilizumab

*Santos Castañeda, MD, PhD**
*Sara Remuzgo-Martínez, PhD**
*Raquel López-Mejías, PhD*
*Fernanda Genre, PhD*
*Jaime Calvo-Alén, MD, PhD*
*Irene Llorente, MD*
*Elena Aurrecoechea, MD, PhD*
*Ana M. Ortiz, MD, PhD*
*Ana Triguero, BSc*
*Ricardo Blanco, MD, PhD*
*Javier Llorca, MD, PhD*
*Miguel A. González-Gay, MD, PhD*

**These authors shared first authorship in this study.*

*Please address correspondence to:*
*Prof. Miguel A. González-Gay,*
*Rheumatology Division,*
*Hospital Universitario Marqués de Valdecilla, IDIVAL,*
*Avenida de Valdecilla, s/n,*
*39008 Santander, Spain.*
*E-mail: miguelaggay@hotmail.com*

*Received on April 12, 2018; accepted in revised form on July 23, 2018.*

*© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2019.*

*The results of this work were partially presented at the 2017 ACR Meeting in San Diego, CA, USA (abstract no. 1400) (View Abstract and Citation Information Online - http://acrabstracts.org/abstract/beneficial-effect-of-anti-il-6-blockade-on-insulinresistance-and-insulin-sensitivity-in-patients-with-rheumatoid-arthritis).*

*Funding: none.*

*Competing interests: M.A. Gonzalez-Gay has served as consultant with Roche and Sanofi-Aventis; the other co-authors have declared no competing interests.*

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition associated with accelerated atherosclerosis and increased risk of cardiovascular (CV) disease (1-5). Patients with RA display a high incidence of metabolic syndrome (6-9). In this regard, insulin resistance (IR), a metabolic abnormality in which peripheral tissues show decreased sensitivity or response to the metabolic actions of insulin, is among the main components of this syndrome (9). A link between inflammation and IR in RA exists (10, 11). It was elegantly confirmed by Dessein *et al*. who demonstrated that the acute phase response was strongly related to decreased insulin sensitivity in patients with RA (12). These investigators showed that the insulin concentration in patients with RA and other inflammatory arthritides was 57% higher than in age and sex-matched controls (13). Similarly, Ferraz-Amaro *et al*. showed that insulin levels were 33% higher in 151 RA patients than in healthy controls (14). Also, insulin concentrations in patients with RA were 41% higher than in age- and sex-matched patients with osteoarthritis (15). Moreover, high C-reactive protein (CRP) levels were associated with IR and hypertension in RA (15).

Impaired pancreatic β-cell function is observed in patients with RA (16, 17). Most studies support the claim that inflammation in RA induces an abnormal glucose metabolism and that this effect is related to the activity of disease and the levels of acute phase reactants (15, 16, 18). Preclinical and clinical studies have demonstrated that the same pro-inflammatory cytokines that are typically dysregulated in RA, such as TNF-α, IL-1, IL-6 and IL-8, participate actively in the pathophysiology of IR in these patients (7, 9, 19). In line with these findings, there is enough evidence demonstrating the positive effect of the blockade of some of these cytokines in the evolution of IR. In this way, the TNF inhibitors infliximab, etanercept and adalimumab have demonstrated a reduction in the IR tests and improvement of insulin sensitivity in patients with RA and other inflammatory joint diseases (20-26). However, as recently pointed out by Ursini et al. (27), this evidence is lesser with other biologic therapies (28).

IL-6 is a pivotal proinflammatory cytokine strongly implicated in the acute phase response (13). Because of that, it is plausible to think that the adequate blockade of IL-6 would lead to improvement of insulin metabolism in patients with active RA. Tocilizumab (TCZ) is a humanised monoclonal antibody that binds to the IL-6 receptor showing a great efficacy in RA naïve or refractory to other therapies (29). However, only a few studies have focused specifically on the potential beneficial effects of TCZ on IR in patients with RA. Most of them included small number of cases and addressed the effect of TCZ after several months of therapy (24, 30).

We previously reported that an infusion of the anti-TNF infliximab in long-standing RA patients yielded a rapid and dramatic reduction of IR along with a significant improvement of insulin sensitivity (20, 21). However, this aspect on the potentially rapid effect of the anti-IL-6 blockade on IR in patients with RA has not been addressed. Due to this, we aimed to determine if an intravenous infusion of TCZ might yield a dramatic improvement of the insulin metabolism in a series of patients with RA undergoing periodic treatment with this biologic agent because of severe disease.

## Patients and methods

### *Patient population*

A series of 50 consecutive non-diabetic patients with RA undergoing periodic treatment with the anti-IL-6 monoclonal antibody-TCZ were assessed. They were recruited from the Rheumatology outpatient clinics of Hospital de La Princesa (Madrid, Spain) and Hospital de Sierrallana (Cantabria, Spain) in 2015. All patients were 18 years of age or older and fulfilled the 1987 and 2010 classification criteria for RA (31, 32).

Since the purpose of the study was to assess the short-term effect of TCZ on insulin metabolism in non-diabetic RA patients treated with this drug, a comparison of the effect of TCZ administration in each patient (before and after) was performed. Because of that, a placebo-controlled group was not included in the assessment. The same procedure

was found acceptable and followed in studies on the short-term effect of the anti-TNF infliximab therapy on the glucose (20) and lipid profile in patients with RA (33). At the time of enrolment, all patients underwent evaluation of their demographic, clinical characteristics, therapies received and clinical and laboratory disease activity parameters. Patients with diabetes, fasting plasma glucose levels >125 mg/dl or current antidiabetic oral drugs, chronic kidney disease (serum creatinine ≥1.3 mg/dl or glomerular filtration rate <60 ml/min) and body mass index (BMI) ≥35 (kg/m$^2$) were not included in the study. Only 3 of the 50 patients were naïve to TCZ at the time of the assessment. In these 3 patients, a 6-week washout period for other biologic systemic therapies was performed. The remaining patients were on periodical treatment with this biologic agent. TCZ (RoActemra®, Roche Laboratories, Spain) was administered intravenously at variable doses ranging between 4 mg and 8 mg/kg every 4–6 weeks. In this regard, at the time of the study, the majority of them were treated with 8 mg/kg of TCZ intravenously every 4 weeks. This series of patients included long-standing RA patients. Because of that, in all cases the monoclonal antibody TCZ was prescribed because of active disease refractory to methotrexate and also in most of cases to other biologic agents. The study protocol was approved by the local institutional ethics committee of every participant center, and it was in accordance with the ethical standards outlined in the Declaration of Helsinki. All patients gave informed consent to participate in this study previous to their inclusion. This study has not been supported by any pharmaceutical company.

*Study protocol*

In all cases, TCZ was administered as an intravenous infusion in a saline solution over 60 minutes. Blood samples were taken after a 12-hour overnight fast between 08:00 am and 10:00 am hours immediately prior to the TCZ infusion (time 0/basal) and 60 minutes after finishing TCZ infusion (60´after). Vital signs were also registered before the infusion, immediately at the end of the infusion and 1 hour later.

Baseline glucose, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured by standard automated methods on every participant center. Erythrocyte sedimentation rate (ESR) was determined using the Westergren method and C-reactive protein (CRP) by latex immuno-turbidimetry. Rheumatoid factor (RF) and anti-citrullinated peptide (Anti-CCP) antibodies were also assessed according to the automated methods on each participant Centre. Serum insulin levels (μU/ml) and serum C peptide levels (ng/mL) were quantified by electrochemiluminescence (Liaison, DiaSorin, Stillwater, MN, USA, or Roche Diagnostics, Switzerland). A commercial immunoassay kit was used to measure serum human IL-6 levels (R&D Systems, D6050; assay sensitivity=0.70 pg/mL; intra-and interassay coefficients of variation were <2.6% and <4.5%, respectively) (R&D Systems Europe, Ltd., Abingdon, UK). Serum levels of IL-6 were measured in samples obtained immediately prior to a TCZ infusion and 60 minutes later. Plasma glucose, insulin, insulin/glucose ratio and C peptide were also assessed again 1 hour after the end of TCZ infusion (60´ after). None of the patients did receive any nutrient before and during infusion, or during the period between the end of TCZ infusion and the second blood sample taken 1 hour after finishing TCZ infusion.

*Assessment of insulin resistance and sensitivity*

While the hyperinsulinemic euglycemic clamp technique is the gold standard for evaluating insulin sensitivity, the Homeostasis Model Assessment (HOMA) for insulin resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) are widely used

**Table I**. Baseline characteristics of 50 patients with rheumatoid arthritis undergoing tocilizumab therapy.

| | |
|---|---|
| Age at the time of disease onset, years, mean ± SD | 47.5 ± 12.6 |
| Age at the time of the study, years, mean ± SD | 60.0 ± 13.9 |
| Women, n (%) | 42 (80%) |
| Disease duration, years, mean ± SD | 12.6 ± 6.4 |
| Rheumatoid factor positive, n (%)* | 34 (69.4%) |
| Anti-CCP antibodies positive, n (%)* | 24 (68.6%) |
| Disease activity | |
| DAS28-ESR, mean ± SD | 3.2 ± 1.3 |
| DAS28-CRP, mean ± SD | 2.7 ± 1.0 |
| Swollen joint count, mean ± SD | 2.0 ± 2.8 |
| Tender joint count, mean ± SD | 4.2 ± 4.4 |
| VAS patient disease activity, mean ± SD | 36.7 ± 21.5 |
| C-reactive protein, mg/dl, mean ± SD | 0.4 ± 0.6 |
| ESR, mm/1$^{st}$ hour, mean ± SD | 14.5 ± 17.0 |
| Platelet count/mm$^3$ at the time of the study, mean ± SD | 213.1 ± 58.7 |
| Metabolic syndrome features | |
| Body mass index, kg/m$^2$, mean ± SD | 26.3 ± 5.4 |
| Hypertension, n (%) | 22 (44%) |
| Systolic blood pressure, mmHg, mean ± SD | 130.3 ± 16.6 |
| Diastolic blood pressure, mmHg, mean ± SD | 73.4 ± 11.4 |
| Triglycerides, mg/dl, mean ± SD | 120.8 ± 78.6 |
| HDL cholesterol, mg/dl, mean ± SD | 66.8 ± 23.7 |
| Glucose, mg/dl, mean ± SD | 91.6 ± 10.0 |
| Insulin, μU/ml, mean ± SD | 10.7 ± 5.7 |
| HOMA-IR, μU mmol/ml, mean ± SD | 2.6 ± 2.0 |
| QUICKI, mean ± SD | 0.3 ± 0.0 |
| Total cholesterol, mg/dl, mean ± SD | 211.8 ± 39.9 |
| LDL cholesterol, mg/dl, mean ± SD | 131.5 ± 54.6 |
| C-peptide, ng/ml, mean ± SD | 3.0 ± 1.2 |
| N. of TCZ doses received prior to the study, mean± SD | 20.7 ± 17.3 |

Anti-CCP: anti citrullinated cyclic peptide antibodies; DAS: disease activity score; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index; LDL: low-density lipoprotein; TCZ: tocilizumab; SD: standard deviation. *At least 2 determinations were required for the analysis of this variable.

**Table II**. Associations between baseline patient characteristics immediately before and after a single anti-IL-6-receptor tocilizumab infusion and HOMA-IR in 50 patients with rheumatoid arthritis.

| Patient characteristics | HOMA-IR pre-infusion | | HOMA-IR post-infusion | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| Age, years | | | | |
| At disease onset | 0.12 | 0.42 | 0.04 | 0.78 |
| At the time of the study | -0.17 | 0.25 | -0.22 | 0.14 |
| Disease duration, years | 0.17 | 0.25 | 0.22 | 0.14 |
| Disease activity | | | | |
| DAS28-ESR | -0.13 | 0.39 | 0.08 | 0.61 |
| DAS28-CRP | -0.26 | 0.09 | -0.07 | 0.67 |
| Swollen joints | -0.17 | 0.26 | -0.21 | 0.15 |
| Tender joints | -0.25 | 0.09 | -0.02 | 0.88 |
| VAS patient disease activity | -0.13 | 0.38 | -0.09 | 0.58 |
| CRP protein, mg/dl at the time of the study | 0.03 | 0.87 | 0.18 | 0.24 |
| ESR, mm/hr at the time of the study | 0.15 | 0.30 | 0.30 | **0.04** |
| Platelet count/mm$^3$ at the time of the study | 0.00 | 0.98 | 0.00 | 0.99 |
| Metabolic syndrome | | | | |
| BMI, kg/m$^2$ | 0.51 | **<0.01** | 0.58 | **<0.01** |
| Basal glucose, mg/dl | 0.40 | **<0.01** | 0.26 | 0.08 |
| Basal insulin, µU/ml | 0.65 | **<0.01** | 0.75 | **<0.01** |
| Triglycerides, mg/dl | 0.07 | 0.66 | 0.47 | **<0.01** |
| Total cholesterol, mg/dl | 0.06 | 0.69 | -0.05 | 0.76 |
| HDL cholesterol, mg/dl | -0.12 | 0.46 | -0.33 | **0.03** |
| LDL cholesterol mg/dl | 0.05 | 0.75 | 0.22 | 0.15 |
| C-peptide, ng/ml | 0.51 | **<0.01** | 0.72 | **<0.01** |
| Systolic BP, mmHg | 0.00 | 0.99 | 0.20 | 0.19 |
| Diastolic BP, mmHg | -0.24 | 0.11 | 0.01 | 0.95 |
| Number of tocilizumab doses received prior to the study | 0.09 | 0.53 | 0.05 | 0.74 |

The data were analysed in simple linear regression models. DAS: disease activity score; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BP: blood pressure; HOMA-IR: homeostasis model assessment of insulin resistance. In bold the values with $p<0.05$.

as noninvasive surrogate markers of IR and insulin sensitivity, respectively (34, 35). Although results of both HOMA and QUICKI are shown in this report, the use of the QUICKI is superior to the HOMA index since the variables are logarithmically transformed (34).

*Statistical analyses*

The results were reported as mean ± standard deviation (SD). For the comparison of normally distributed variables between groups, Student's *t*-test was used. Correlation of HOMA-IR and QUICKI prior to TCZ (basal) and 60 minutes after the end of the infusion with selected continuous variables was performed adjusting for age, sex and disease duration via estimation of the Pearson partial correlation coefficient (r). Statistical analysis was calculated using STATA 12/SE (StataCorp, College Station, TX, USA). Differences statistically significant were considered at $p<0.05$.

## Results

*Clinical characteristics of the patients*

Epidemiological and clinical characteristics of the patients included in this study are shown in Table I. There was a predominance of women (80%) with a mean duration of the disease of 12.6 years. Almost 70% were RF and/or anti-CCP antibodies positive. The mean DAS28 at the time of assessment was 3.2, which was the result of the prolonged use of TCZ in these patients, who initiated treatment with this biologic agent because of severe and active disease. In this regard, 37 of the 50 patients had received at least six monthly intravenous infusions of TCZ and the mean number of monthly intravenous infusions received by the patients of this series was 20.7.

*Relationship between HOMA-IR and disease variables*

Table II shows the main correlations between HOMA-IR and the different variables assessed in the study. As expected, there was a positive association of HOMA-IR with BMI, insulin levels and C-peptide values immediately before and 1 hour after the end of TCZ administration. A positive correlation between HOMA-IR and ESR and triglycerides was also observed following TCZ infusion.

*Relationship between QUICKI and disease variables*

The main correlations between clinical variables and QUICKI- insulin sensitivity before and 1 hour after the end of TCZ infusion are shown in Table III. BMI, insulin and C-peptide levels showed a strong negative association with QUICKI. Also, a negative significant correlation between baseline ESR and QUICKI was observed.

*Effect of the tocilizumab infusion on glucose metabolism*

Following TCZ administration, there was a statistically significant reduction of insulin resistance (HOMA-IR: mean± standard deviation immediately before: 2.62±2.03 *vs*. 1.65±1.15 1 hour after the end of the infusion, $p<0.01$) and a statistically significant increase of insulin sensitivity (QUICKI immediately before 0.34±0.03 *vs*. 0.37±0.04 1 hour after the end of tocilizumab infusion, $p<0.01$) (Table IVA). Figs. 1A and 1B show the changes in HOMA-IR and QUICKI- insulin sensitivity experienced by each individual. These figures confirm that the reduction of IR and the improvement of insulin sensitivity were reproducible in the vast majority of the individuals assessed in the study. Also, as shown in Table IVA and Figure 2, there was a rapid and statistically significant reduction of insulin serum levels and insulin/glucose ratio following TCZ infusion. Moreover, TCZ intravenous infusion yielded a significant decrease of C peptide levels (3.01±1.23 ng/ml prior to TCZ infusion *vs*. 2.56±1.18 ng/ml 1 hour after the end of TCZ infusion; $p<0.01$). When splitting the sample into two groups according to their basal HOMA-IR, similar trends were found in both subsamples, although changes in patients with ba-

**Table III**. Associations between baseline patient characteristics immediately before and after a single anti-IL-6-receptor tocilizumab infusion and QUICKI (insulin sensitivity) in 50 patients with rheumatoid arthritis.

| Patient characteristics | QUICKI pre-infusion | | QUICKI post-infusion | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| Age, years | | | | |
| At disease onset | -0.07 | 0.65 | -0.05 | 0.71 |
| At the time of the study | 0.18 | 0.23 | 0.00 | 0.99 |
| Disease duration, years | -0.18 | 0.23 | 0.00 | 0.99 |
| Disease activity | | | | |
| DAS28-ESR | -0.07 | 0.63 | -0.20 | 0.20 |
| DAS28-CRP | 0.15 | 0.34 | 0.03 | 0.85 |
| Swollen joints | 0.23 | 0.12 | 0.21 | 0.16 |
| Tender joints | 0.11 | 0.44 | -0.03 | 0.84 |
| VAS patient disease activity | 0.10 | 0.53 | 0.02 | 0.91 |
| CRP protein, mg/dl at the time of the study | -0.23 | 0.12 | -0.17 | 0.26 |
| ESR, mm/hr at the time of the study | -0.32 | **0.03** | -0.30 | **0.04** |
| Platelet count/mm$^3$ at the time of the study | 0.03 | 0.84 | 0.01 | 0.96 |
| Metabolic syndrome | | | | |
| BMI, kg/m$^2$ | -0.62 | **<0.01** | -0.57 | **<0.01** |
| Basal glucose, mg/dl | -0.24 | 0.09 | -0.26 | 0.07 |
| Basal insulin, µU/ml | -0.90 | **<0.01** | -0.71 | **<0.01** |
| Triglycerides, mg/dl | -0.18 | 0.24 | -0.29 | 0.05 |
| Total cholesterol, mg/dl | -0.03 | 0.83 | 0.07 | 0.65 |
| HDL cholesterol, mg/dl | 0.14 | 0.36 | 0.23 | 0.14 |
| LDL cholesterol mg/dl | -0.14 | 0.37 | -0.15 | 0.33 |
| C-peptide, ng/ml | -0.69 | **<0.01** | -0.61 | **<0.01** |
| Systolic BP, mmHg | 0.02 | 0.89 | -0.06 | 0.69 |
| Diastolic BP, mmHg | 0.12 | 0.43 | 0.10 | 0.49 |
| Number of tocilizumab doses received prior to the study | -0.23 | 0.13 | 0.00 | 1.00 |

The data were analysed in simple linear regression models. DAS: disease activity score; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BP: blood pressure; QUICKI: quantitative insulin sensitivity check index. In bold the values with $p<0.05$.

sal HOMA-IR over the median were stronger (Table IVB-C). Furthermore, a non-significant increase of the levels of IL-6 following the administration of TCZ was observed (Table IVA-B-C).

## Discussion

The prevalence of metabolic syndrome, IR and diabetes is increased in patients with RA and other inflammatory joint diseases (6, 8, 9, 36, 37). A sustained inflammation maintained over time predisposes to IR and endothelial dysfunction, an early step in the accelerated atherogenesis process that occurs in RA (38, 39). In this regard, there is a close relationship between inflammation, acute phase reactants, subclinical atherosclerosis and IR (6, 7, 13, 15). Proinflammatory cytokines, such as TNF and IL-6, are implicated in RA and play an important role in the development of endothelial dysfunction (2, 38, 39). Interestingly, anti-TNF agents have shown to improve the endothelial function of patients with RA (40, 41). Besides, several studies have confirmed both short-term and long-term beneficial effect of anti-TNF therapy on IR in patients with RA (20-26). Since TCZ shows a great efficacy as an anti-inflammatory agent to be used in patients with severe RA, it is plausible to think that TCZ may also have a favourable effect on the mechanisms associated with IR and atherosclerosis in patients with RA. Further supporting this, and in keeping with the data reported by Dessein *et al*. (13, 15), Chung *et al*. confirmed that the HOMA-IR index was significantly and positively correlated with IL-6 in patients with RA (42). However, there are few studies addressing the effect of the IL-6 blockade on the glucose metabolism in RA. Notwithstanding, such studies evaluated the effect of TCZ after several months of therapy. This prompted us to assess if the effect of the anti-IL-6 receptor blockade mediated by TCZ on insulin metabolism could occur soon after the administration of this biologic agent.

The present study shows for first time that the intravenous administration of TCZ yields a rapid and dramatic reduction of IR in patients with severe RA. Such a beneficial effect was also associated with a rapid improvement of insulin sensitivity in these patients. This effect of TCZ was stronger in patients with more severe IR at baseline.

Furthermore, and in accordance with the relationship of IR and inflammation in RA (10, 11), in our study the levels of ESR showed a statistically significant positive correlation with the HOMA-IR after the infusion of TCZ. This link between inflammation and glucose abnormalities was further supported by the statistically significant negative correlation between the baseline levels of ESR and QUICKI before and after the infusion of TCZ. Further supporting these data, a significant correlation of insulin levels with both HOMA-IR and QUICKI was disclosed in our series of patients before and after TCZ infusion. On the other hand, it is well-known that obesity is associated with IR. With respect to this, we observed a positive correlation of HOMA-IR with BMI and a negative correlation with QUICKI before and after the infusion of TCZ. Moreover, in our study we observed an increase of the levels of IL-6 following TCZ administration. Although this finding speaks in favour of an effective blockade of the IL-6 receptor mediated by TCZ, the difference did not achieve statistically significance, probably because of the short period of time elapsed between the two determinations.

In most cases, previous studies that evaluated the effect of IL-6 blockade on the glucose metabolism in RA included a small number of patients. In this regard, Schultz *et al*. studied insulin sensitivity in 11 non-diabetic patients with RA treated with intravenous TCZ at a dose of 8 mg/kg body weight every 4 weeks (30). These authors found a significant reduction of HOMA-IR after 3 months of therapy. Also, Chen *et al*. assessed 24 RA patients who received

**Table IVA.** Differences between basal (time 0) and post-infusion (time 60 minutes after the end of a single tocilizumab infusion) levels of glucose and insulin, insulin/glucose ratio, HOMA-IR, QUICKI, and C-peptide and IL-6 levels.

| | Basal (time 0) Mean ± SD | Post-infusion (time 60 min) Mean ± SD | *p* |
|---|---|---|---|
| Plasma glucose (mg/dl) | 91.58 ± 10.04 | 89.32 ± 10.96 | 0.06 |
| Serum insulin (μU/ml) | 10.65 ± 5.75 | 7.61 ± 5.08 | **<0.01** |
| Insulin/glucose ratio | 0.18 ± 0.07 | 0.09 ± 0.06 | **<0.01** |
| HOMA-IR | 2.62 ± 2.03 | 1.65 ± 1.15 | **<0.01** |
| QUICKI | 0.34 ± 0.03 | 0.37 ± 0.04 | **<0.01** |
| C-peptide (ng/ml) | 3.01 ± 1.23 | 2.56 ± 1.18 | **<0.01** |
| IL-6 (pg/ml) | 55.12 ± 66.14 | 62.36 ± 55.57 | 0.18 |

SD: standard deviation; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index.

**Table IVB.** Differences between basal (time 0) and post-infusion (time 60 minutes after the end of a single tocilizumab infusion) levels of glucose and insulin, insulin/glucose ratio, HOMA-IR, QUICKI, and C-peptide and IL-6 levels. Patients with basal HOMA-IR over the median.

| | Basal (time 0) Mean ± SD | Post-infusion (time 60 min) Mean ± SD | *p* |
|---|---|---|---|
| Plasma glucose (mg/dl) | 94.96 ± 10.48 | 92.68 ± 11.55 | 0.22 |
| Serum insulin (μU/ml) | 14.93 ± 5.28 | 10.48 ± 5.64 | **<0.01** |
| Insulin/glucose ratio | 0.16 ± 0.07 | 0.12 ± 0.07 | **<0.01** |
| HOMA-IR | 3.89 ± 2.30 | 2.33 ± 1.26 | **<0.01** |
| QUICKI | 0.32 ± 0.01 | 0.35 ± 0.03 | **<0.01** |
| C-peptide (ng/ml) | 3.63 ± 1.26 | 3.10 ± 1.36 | **<0.01** |
| IL-6 (pg/ml) | 49.3 ± 65.76 | 61.58 ± 64.65 | 0.15 |

SD: standard deviation; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index.

**Table IVC.** Differences between basal (time 0) and post-infusion (time 60 minutes after the end of a single tocilizumab infusion) levels of glucose and insulin, insulin/glucose ratio, HOMA-IR, QUICKI, and C-peptide and IL-6 levels. Patients with basal HOMA-IR below the median.

| | Basal (time 0) Mean ± SD | Post-infusion (time 60 min) Mean ± SD | *p* |
|---|---|---|---|
| Plasma glucose (mg/dl) | 88.20 ± 8.50 | 85.96 ± 9.40 | 0.17 |
| Serum insulin (μU/ml) | 6.46 ± 2.00 | 4.86 ± 2.25 | **<0.01** |
| Insulin/glucose ratio | 0.07 ± 0.03 | 0.06 ± 0.03 | **<0.01** |
| HOMA-IR | 1.40 ± 0.42 | 1.00 ± 0.46 | **<0.01** |
| QUICKI | 0.37 ± 0.02 | 0.39 ± 0.03 | **<0.01** |
| C-peptide (ng/ml) | 2.40 ± 0.84 | 2.06 ± 0.72 | **<0.01** |
| IL-6 (pg/ml) | 60.92 ± 67.35 | 63.14 ± 48.51 | 0.75 |

SD: standard deviation; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index.

TCZ at a dose of 4 mg/kg intravenously once monthly during the first 3 months and then 8 mg/kg once monthly (24). A significant reduction was observed in HOMA-IR at week 24 (2.97±0.38 *vs*. 1.99±0.25; $p<0.05$) (24). In contrast, two studies did not confirm a beneficial effect of the anti-IL-6 receptor blockade on IR. With respect to this, Makrilakis *et al*. assessed the effect of TCZ on IR in 19 patients with RA (two of them with type 2 diabetes) before and after 6 months of intravenous treatment with this biologic agent (8 mg/kg, every 4 weeks) (43). Although patients from this study exhibited a decrease of IR, such a reduction of HOMA-IR did not achieve statistical significance (baseline HOMA-IR: 5.02±8.14 *vs*. 2.34±2.44 at month 6) (43). Also, in keeping with our results, the mean insulin level in this series of 19 RA patients showed a reduction following the treatment with TCZ (baseline insulin level 150.6±226.18 *vs*. 74.86±73.93). However, the reduction of insulin levels was not statistically significant (43). Based on the baseline HOMA-IR, patients included in this study and our individuals were different and it may be the reason for the discrepancy in the results. However, our disease population appeared to be similar to their 6 months population (43). With respect to this, baseline levels of HOMA-IR in this series were in a range of IR state (mean basal HOMA-IR: 5.02), which was markedly higher than that found in our series of 50 non-diabetic RA patients who had lower baseline HOMA-IR levels (mean HOMA-IR before TCZ infusion in our series: 2.62). Another study yielding negative results was conducted by Tournadre *et al*. (44). These authors initially included 21 patients but only data of 15 of them were available after 6 months of TCZ therapy (44). To our surprise, the mean HOMA-IR at month 6 was higher than at baseline in this series (2.1±1.1 *vs*. 3.9±5.1). In contrast to the former studies that in most cases included small series of patients, it is worth mentioning the results found in the phase III trial TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) study that included a larger cohort of RA patients (45). With respect to this, in a subanalysis of this study, 328 patients with RA were assessed for IR before and after 24 weeks of intravenous TCZ therapy (8 mg/kg/infusion). Patients were randomised to TCZ (n=221) or placebo (n=107). Only the subgroup of TCZ-treated patients experienced a statistically significant reduction of HOMA-IR (mean change –1.97, $p<0.01$). It was not the case for the placebo group (mean change -0.77, $p=0.33$) (45). Although it is said that QUICKI has better reproducibility than HOMA-IR (34, 46), there is no information related to the effect of TCZ on QUICKI in patients with RA.

The reduction of IR in our RA patients following infusion of TCZ cannot be compared to the reduction of IR in patients treated with anti-TNF, as previously reported (20), since the latter was performed in RA patients with severe

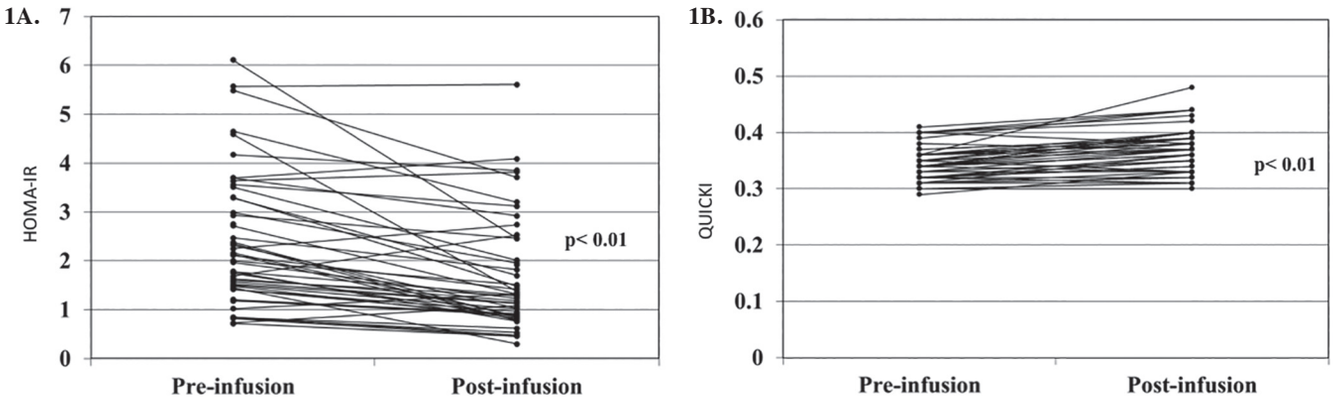



**Fig. 1A.** Changes in HOMA-IR in each patient following tocilizumab infusion. **1B.** Changes in QUICKI in each patient following tocilizumab infusion.

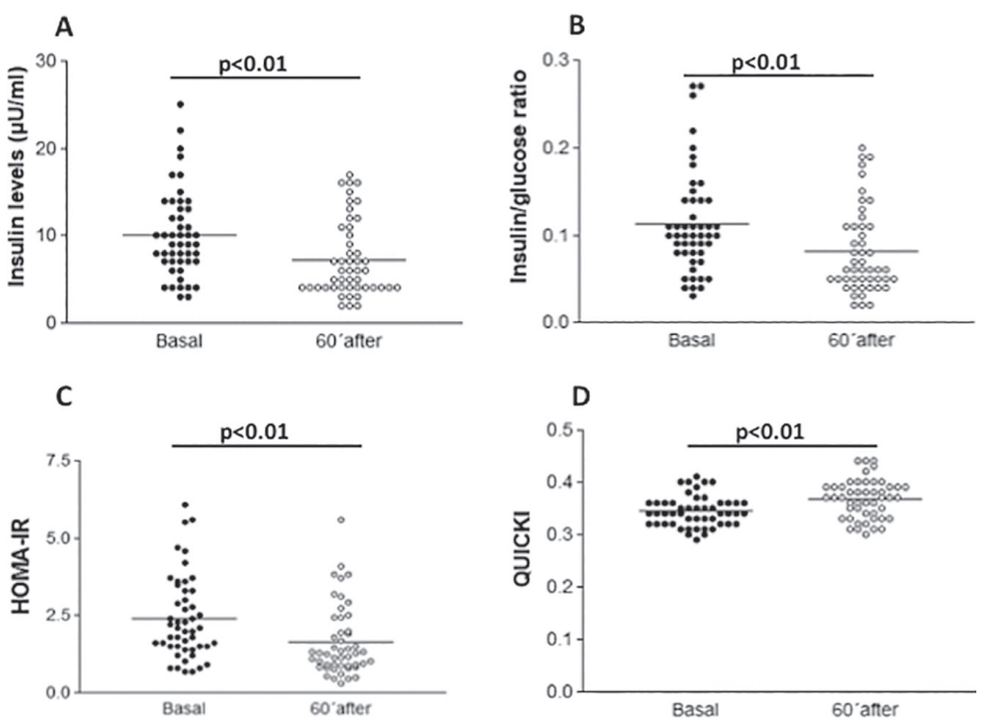



**Fig. 2.** Statistically significant reduction of insulin serum levels, insulin/glucose ratio, HOMA-IR and QUICKI following tocilizumab intravenous infusion in a series of 50 patients with severe rheumatoid arthritis.

disease who received anti-TNF therapy more than ten years ago. Anti-TNF-infliximab was the first biologic agent used in those patients. In contrast, many of the patients from the present series had previously been treated with other biologic agents prior to TCZ. Management of RA has changed over the last two decades and it may explain that metabolic abnormalities in patients with RA may be less severe than in the past decade. Most patients included in the TCZ study had received conventional therapy very soon after the onset of the disease. The mean baseline DAS28-ESR in the series of anti-TNF-infliximab treated was 4.4 whereas in the present series of TCZ treated patients it was 3.2. Moreover, anti-TNF-treated patients had worse baseline HOMA-IR and QUICKI results. Because of that, it is difficult to compare the results of both studies. Nevertheless, in both cases a beneficial effect was observed.

There are a number of limitations of our study. First, we assessed the immediate effect of a TCZ infusion. However, we did not evaluate the effect of the TCZ infusion later (*e.g.* 24 hours after the infusion). Moreover, we did not study the influence of TCZ therapy on the CV outcome of our patients since we did not perform a prospective follow-up of this cohort. Finally, our *p*-values were not corrected for the multiple comparisons performed.

In conclusion, our data confirm a rapid beneficial effect of TCZ on IR and insulin sensitivity in non-diabetic patients with severe RA. It may support the long-term use of drugs that act blocking IL-6 to reduce the mechanisms implicated in the development of atherosclerosis in these patients. Our results may be of potential clinical relevance since we disclose that the administration of TCZ leads to an improvement of HOMA-IR and QUICKI according to reference values (47). In addition, it is plausible to think that a pre-selection of patients based on HOMA-IR values before the onset of TCZ treatment would be helpful to predict who would benefit most from the treatment.

## Acknowledgements

We thank all the participating patients, who generously collaborated in the study and also the nurses from the different hospitals who helped us.

## References

1. AVINA-ZUBIETA JA, THOMAS J, SADATSAFAVI M, LEHMAN AJ, LACAILLE D: Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012; 71: 1524-9.
2. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35: 8-17.
3. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, LOPEZ-DIAZ MJ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 125-32.
4. LÓPEZ-MEJÍAS R, CASTAÑEDA S, GONZÁLEZ-JUANATEY C *et al*.: Cardiovascular risk assessment in patients with rheumatoid arthritis: The relevance of clinical, genetic and serological markers. *Autoimmun Rev* 2016; 15: 1013-30.
5. CROWSON CS, ROLLEFSTAD S, IKDAHL E *et al*.: Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77: 48-54.
6. FERRAZ-AMARO I, GONZÁLEZ-JUANATEY C, LÓPEZ-MEJIAS R, RIANCHO-ZARRABEITIA L, GONZÁLEZ-GAY MA: Metabolic syndrome in rheumatoid arthritis. *Mediators Inflamm* 2013; 2013: 710928.
7. KEREKES G, NURMOHAMED MT, GONZALEZ-GAY MA *et al*.: Rheumatoid arthritis and metabolic syndrome. *Nat Rev Rheumatol* 2014; 10: 691-6.
8. CASTAÑEDA S, NURMOHAMED MT, GONZÁLEZ-GAY MA: Cardiovascular disease in inflammatory rheumatic diseases. *Best Pract Res Clin Rheumatol* 2016; 30: 851-69.
9. GILES JT, DANIELIDES S, SZKLO M *et al*.: Insulin resistance in rheumatoid arthritis: disease-related indicators and associations with the presence and progression of subclinical atherosclerosis. *Arthritis Rheumatol* 2015; 67: 626-36.
10. SVENSON KLG, POLLARE T, LITHELL H, HALLGREN R: Impaired Glucose Handling in Active Rheumatoid-Arthritis-Relationship to Peripheral Insulin Resistance. *Metabolism* 1988; 37: 125-30.
11. URSINI F, D'ANGELO S, RUSSO E *et al*.: Serum complement C3 strongly correlates with whole-body insulin sensitivity in rheumatoid arthritis. *Clin Exp Rheumatol* 2017; 35: 18-23.
12. DESSEIN PH, JOFFE BI, STANWIX AE: Inflammation, insulin resistance, and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. *J Rheumatol* 2003; 30: 1403-5.
13. DESSEIN PH, JOFFE BI, STANWIX A, BOTHA AS, MOOMAL Z: The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. *J Rheumatol* 2002; 24: 462-6.
14. FERRAZ-AMARO I, LÓPEZ-MEJIAS R, TEJERA-SEGURA B *et al*.: Amylin in the insulin resistance of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 421-7.
15. DESSEIN PH, STANWIX AE, JOFFE BI: Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. *Arthritis Res* 2002; 4: R5.
16. DESSEIN PH, JOFFE BI: Insulin resistance and impaired beta cell function in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 2765-75.
17. FERRAZ-AMARO I, GARCÍA-DOPICO JA, MEDINA-VEGA L, GONZÁLEZ-GAY MA, DÍAZ-GONZÁLEZ F: Impaired beta cell function is present in nondiabetic rheumatoid arthritis patients. *Arthritis Res Ther* 2013; 15: R17.
18. CHUNG C, OESER A, SOLUS JF *et al*.: Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. *Arthritis Rheum* 2008; 58: 2105-12.
19. PI H, ZHOU H, JIN H, NING Y, WANG Y: Abnormal glucose metabolism in rheumatoid arthritis. *Biomed Res Int* 2017; 2017: 9670434.
20. GONZALEZ-GAY MA, DE MATIAS JM, GONZALEZ-JUANATEY C *et al*.: Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 83-6.
21. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MIRANDA-FILLOY JA, LLORCA J: Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. *Ann N Y Acad Sci* 2010; 1193: 153-9.
22. STAVROPOULOS-KALINOGLOU A, METSIOS GS, PANOULAS VF, NIGHTINGALE P, KOUTEDAKIS Y, KITAS GD: Anti-tumour necrosis factor alpha therapy improves insulin sensitivity in normal-weight but not in obese patients with rheumatoid arthritis. *Arthritis Res Ther* 2012; 14: R160.
23. STAGAKIS I, BERTSIAS G, KARVOUNARIS S *et al*.: Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. *Arthritis Res Ther* 2012; 14: R141.
24. CHEN DY, CHEN YM, HSIEH TY, HSIEH CW, LIN CC, LAN JL: Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. *Arthritis Res Ther* 2015; 17: 52.
25. BURSKA AN, SAKTHISWARY R, SATTAR N: Effects of tumour necrosis factor antagonists on insulin sensitivity/resistance in rheumatoid arthritis: a systematic review and meta-analysis. *PLoS One* 2015; 10: e0128889.
26. BISSELL LA, HENSOR EM, KOZERA L *et al*.: Improvement in insulin resistance is greater when infliximab is added to methotrexate during intensive treatment of early rheumatoid arthritis-results from the IDEA study. *Rheumatology* (Oxford) 2016; 55: 2181-90.
27. URSINI F, RUSSO E, RUSCITTI P, GIACOMELLI R, DE SARRO G: The effect of non-TNF-targeted biologics and small molecules on insulin resistance in inflammatory arthritis. *Autoimmun Rev* 2018; 17: 399-404.
28. URSINI F, RUSSO E, LETIZIA HRIBAL M *et al*.: Abatacept improves whole-body insulin sensitivity in rheumatoid arthritis: an observational study. *Medicine* (Baltimore) 2015; 94: e888.
29. ZHANG X, PECK R: Clinical pharmacology of tocilizumab for the treatment of patients with rheumatoid arthritis. *Expert Rev Clin Pharmacol* 2011; 4: 539-58.
30. SCHULTZ O, OBERHAUSER F, SAECH J *et al*.: Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS One* 2010; 5: e14328.
31. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
32. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
33. VIS M, NURMOHAMED MT, WOLBINK G *et al*.: Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32:252-5.
34. KATZ A, NAMBI SS, MATHER K *et al*.: Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000; 85: 2402-10.
35. GORDILLO-MOSCOSO A, VALADEZ-CASTILLO JF, MANDEVILLE PB, HERNANDEZ-SIERRA JF: Comparison of equivalence and determination of diagnostic utility of min-mod and clamp methods for insulin resistance in diabetes free subjects: a meta-analysis. *Endocrine* 2004; 25: 259-63.
36. CHUNG CP, OESER A, SOLUS JF *et al*.: Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2008; 196: 756-63.
37. ZHANG J, FU L, SHI J *et al*.: The risk of metabolic syndrome in patients with rheumatoid arthritis: a meta-analysis of observational studies. *PLoS One* 2013; 8: e78151.
38. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Inflammation and endothelial dysfunction in rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 115-7.
39. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MARTIN J, LLORCA J: Endothelial dysfunction, carotid intima-media thickness, and accelerated atherosclerosis in rheumatoid arthritis. *Semin Arthritis Rheum* 2008; 38: 67-70.
40. GONZALEZ-JUANATEY C, LLORCA J, SANCHEZ-ANDRADE A, GARCIA-PORRUA C, MARTIN J, GONZALEZ-GAY MA: Short-term adalimumab therapy improves endothelial

function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006; 24: 309-12.

41. GONZALEZ-JUANATEY C, VAZQUEZ-RODRIGUEZ TR, MIRANDA-FILLOY JA *et al*.: Anti-TNF-alpha-adalimumab therapy is associated with persistent improvement of endothelial function without progression of carotid intima-media wall thickness in patients with rheumatoid arthritis refractory to conventional therapy. *Mediators Inflamm* 2012; 2012: 674265.
42. CHUNG CP, OESER A, SOLUS JF *et al*.: Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. *Arthritis Rheum* 2008; 58: 2105-12.
43. MAKRILAKIS K, FRAGIADAKI K, SMITH J, SFIKAKIS PP, KITAS GD: Interrelated reduction of chemerin and plasminogen activator inhibitor-1 serum levels in rheumatoid arthritis after interleukin-6 receptor blockade. *Clin Rheumatol* 2015; 34: 419-27.
44. TOURNADRE A, PEREIRA B, DUTHEIL F *et al*.: Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. *J Cachexia Sarcopenia Muscle* 2017; 8: 639-46.
45. MIRJAFARI H, WANG J, KLEARMAN M, HARARI O, BRUCE I: Insulin resistance is improved by Tocilizumab therapy in rheumatoid arthritis: results from the TOWARD study. *Ann Rheum Dis* 2013; 72: 414-5.
46. SARAFIDIS PA, LASARIDIS AN, NILSSON PM *et al*.: Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. *J Hum Hypertens* 2007; 21: 709-16.
47. ASCASO JF, PARDO S, REAL JT, LORENTE RI, PRIEGO A, CARMENA R: Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 2003; 26: 3320-5.