

Abatacept Improves Whole-Body Insulin Sensitivity in Rheumatoid Arthritis

An Observational Study

Francesco Ursini, MD, Emilio Russo, Marta Letizia Hribal, PhD, Daniele Mauro, MD, Francesca Savarino, MD, Caterina Bruno, MD, Cesare Tripolino, MD, Mariangela Rubino, MD, Saverio Naty, MD, and Rosa Daniela Grembiale

Abstract: Rheumatoid arthritis (RA) is characterized by increased insulin resistance, a well-known risk factor for diabetes and cardiovascular diseases. The aim of the present study was to evaluate the effect of abatacept on insulin sensitivity in RA patients with moderate to severe disease despite treatment with methotrexate.

Fifteen RA patients were recruited for the present study. Patients were evaluated at time 0 and after 6 months of the treatment with i.v. abatacept at the dosage recommended for weight range. Evaluation included oral glucose tolerance test (OGTT) at both time points. Insulin sensitivity was estimated with insulin sensitivity index (ISI) by Matsuda, a measure of whole-body insulin sensitivity.

ISI significantly increased after the treatment with abatacept from 3.7 ± 2.6 to 5.0 ± 3.2 ($P = 0.003$) with a mean difference of 1.23. Analysis of glucose and insulin values during OGTT revealed a reduction of both glucose (303.9 ± 73.4 mg/dL min versus 269.2 ± 69.5 mg/dL min, $P = 0.009$) and insulin (208.4 ± 119.7 mg/dL min versus 158.0 ± 95.3 mg/dL min, $P = 0.01$) area under the curves (AUCs). Accordingly also glycated hemoglobin significantly improved ($5.5 \pm 0.4\%$ versus $5.3 \pm 0.3\%$, $P = 0.04$). No significant differences were found for measures of β -cell function insulinogenic index (1.11 ± 1.19 versus 1.32 ± 0.82 , $P = 0.77$) and oral disposition index (2.0 ± 5.4 versus 6.0 ± 6.0 , $P = 0.25$).

Treatment with abatacept seems to be able to improve whole-body insulin sensitivity in RA patients without affecting β -cell function.

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Abbreviations: A1c = glycated hemoglobin, BMI = body mass index, DAS28 = disease activity score including 28 joints, DMARD = disease-modifying antirheumatic drug, ESR = erythrocyte

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From the Department of Medical and Surgical Sciences (FU, MLH, DM, FM, CB, CT, MR, SN, RDG); Science of Health Department, University of Catanzaro, Catanzaro, Italy (ER).

Correspondence: Rosa Daniela Grembiale, Department of Rheumatology, University of Catanzaro, "Magna Graecia", viale Europa, 88100 Catanzaro, Italy (e-mail: rheumatology@unicz.it).

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sedimentation rate, EULAR = European League Against Rheumatism, HDL = high density lipoprotein, hs-CRP = high sensitivity C reactive protein, IGI = insulinogenic index, IR = insulin resistance, ISI = insulin sensitivity index, LDL = low density lipoprotein, MS = metabolic syndrome, ODI = oral disposition index, OGTT = oral glucose tolerance test, RA = rheumatoid arthritis, RF = rheumatoid factor, TNF- α = tumor necrosis factor alpha, Treg = regulatory T cells.

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by an increased cardiovascular diseases risk, estimated to be about 50% greater when compared to the general population.¹ The magnitude of this risk could be considered similar to that conferred by type 2 diabetes mellitus.^{2,3} This phenomenon has been attributed to a synergy between underdiagnosed traditional risk factors and inflammatory disease activity.⁴ The importance to recognize and manage cardiovascular disease risk in RA patients has been emphasized by the European League Against Rheumatism (EULAR), that in 2010 published its recommendations.⁵

Insulin resistance (IR) is typically defined as decreased sensitivity or responsiveness to metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production. IR is now a well-recognized cardiovascular risk factor.^{6,7} Although IR is considered to be a core mechanism of metabolic syndrome (MS), IR even in the absence of an MS phenotype is per se correlated with cardiovascular events.⁸ Improvement of IR with lifestyle intervention lowers the risk of future diabetes⁹ and decreases cardiovascular mortality.¹⁰ In addition, pharmacological intervention with insulin-sensitizing agents, such as thiazolidinediones and metformin, reduces the risk of conversion to type 2 diabetes in individuals at increased risk.¹¹

The glucose clamp technique, originally developed by DeFronzo et al,¹² is widely accepted as the reference standard for directly determining in vivo insulin sensitivity in humans. However, this technique is of limited utility in clinical setting or large studies, because it is time consuming, expensive, and requires experienced operators. For these reasons, simple surrogate indexes of insulin sensitivity/resistance calculated from fasting state values such as Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)¹³ or from dynamic testing, such as Matsuda Index,¹⁴ are considered reliable quantitative tools that can be easily applied in almost every setting, including epidemiological studies, large clinical trials, clinical research investigations, and clinical practice.

RA has been epidemiologically correlated with an elevated prevalence of MS¹⁵ independently of corticosteroids

exposure,¹⁶ and the coexistence of RA with MS appears to be associated with a higher disease activity.^{17,18}

A strict connection between inflammation and IR has been uncovered in the last years.^{19,20} Tumor necrosis factor- α (TNF- α), a proinflammatory cytokine involved in the pathophysiology of RA, has been demonstrated to be involved in this link.^{21,22}

Supporting these evidences, anti-TNF- α medications, such as infliximab, have been reported to improve IR in RA patients.^{23,24}

Abatacept (CTLA4-Ig) is a novel biologic agent approved for the treatment of RA, specifically designed to interfere with T-cells costimulation. Abatacept is considered safe and effective in both clinical trials and the real-world setting, also in patients with comorbidities.²⁵ However, emerging pleiotrophic effect of this molecule are arising from literature. Abatacept has been demonstrated to improve proteinuria in B7-1 positive kidney disease.²⁶ We have recently described a case of dramatic improvement in IR in an RA patient after short-term treatment with abatacept.²⁷ Following this single observation, we decided to start this observational study, with the aim to evaluate the effect of abatacept on insulin sensitivity in RA patients with moderate to severe disease despite methotrexate.

METHODS

Patients

The study protocol was approved by the local ethics committee (Comitato Etico Azienda Ospedaliera Mater Domini, Catanzaro, Italy). For the present study 15 RA patients (8 males and 7 females), eligible for treatment with abatacept (Orencia), were recruited at Rheumatology Outpatient Clinic, Department of Medical and Surgical Sciences, University of Catanzaro, Catanzaro, Italy. All patients satisfied the 2010 ACR/EULAR classification criteria for RA.²⁸ Informed consent was obtained from all patients involved in the present study.

Inclusion criteria were predefined as follows: moderate to severe disease activity despite treatment with disease-modifying antirheumatic drugs (DMARDs), stable treatment with methotrexate, or other DMARDs. Exclusion criteria were predefined as a past diagnosis of diabetes mellitus, polycystic ovary syndrome, infectious, or neoplastic diseases; current treatment with steroids both oral and intraarticular; past treatment with other biologics (ie, anti-TNF- α agents); and past or current treatment with insulin-sensitizing agents (ie, metformin or peroxisome proliferator-activated receptor agonists).

Study Protocol

Given the observational design of our study, all subjects recruited were clinically eligible for the treatment with abatacept because of inadequate response to methotrexate and/or other DMARDs. Patients underwent baseline evaluation (T0) before starting treatment with abatacept. Baseline evaluation comprised anthropometric measurements, disease activity assessment, laboratory evaluation, and insulin sensitivity evaluation as described below. Patients were subsequently treated with abatacept, at the dosage recommended by manufacturer for weight range.²⁹ After 6 months of treatment (T6), patients were reassessed with the same evaluation schedule.

Anthropometric Measurements

Height and weight were measured with patients wearing light clothing and no shoes, to the nearest 0.1 cm and 0.1 kg,

respectively. Body mass index (BMI) was calculated with the standard formula:

$$\text{BMI} = \text{Weight} / \text{Height}^2$$

Waist circumference was assessed with a flexible tape at mid-point between the lowest rib margin and the iliac crest. Blood pressure was measured on the left arm with a mercury sphygmomanometer, with the patient supine and after 5 minutes of rest.

Disease Activity

The disease activity score including 28 joints (DAS28-CRP) was used, evaluating the number of swollen joints count, number of tender joint count (TJC), the patients' global assessment of health measured on a visual analogic scale (global health-visual analogic scale, range 0–100 mm), and high sensitivity C-reactive protein plasma concentration (hs-CRP, mg/L). A score of DAS28-CRP between 2.6 and 3.2 indicates low disease activity, >3.2– \leq 5.1 moderate, and >5.1 high disease activity.³⁰ EULAR response criteria were used to classify patients as good, moderate, or poor responders.³¹

Laboratory Evaluation

After overnight fasting, blood samples were obtained for laboratory evaluation. Plasma glucose, total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), creatinine, uric acid, alanine aminotransferase, and aspartate aminotransferase were measured with automated chemistry analyzer (Cobas 6000/Cobas e411, Roche Diagnostics). Glycated hemoglobin (A1c) was measured by high-performance liquid chromatography (ADAMS A1c, HA-8180, Arkray). Plasma concentration of insulin was determined by chemiluminescence test (Centaur, Siemens HealthCare). Erythrocyte sedimentation rate (ESR) was analyzed by capillary photometry (Test 1, Alifax). hs-CRP was measured by immunonephelometry (CardioPhase hsCRP, Siemens HealthCare, Munich, Germany). Rheumatoid Factor (RF) was analyzed by nephelometry (BN II system, Siemens HealthCare). Anticyclic citrullinated peptide antibodies were analyzed with chemiluminescent immunoassay (Zenit RA CCP, Menarini Diagnostics).

Oral Glucose Tolerance Test (OGTT) and Insulin Sensitivity

A standard OGTT was performed in all patients before and after 6 months of the treatment. The test was performed according to the recommendation of World Health Organization.³²

Briefly, after overnight fasting, the patient was invited to drink a solution with 75 g of anhydrous glucose dissolved in 200 mL of water over a time of 5 minutes; blood samples were collected at time 0, 30, 60, 90, and 120 minutes, and plasma glucose and insulin concentrations were measured.

Insulin sensitivity index (ISI) was calculated with the equation proposed by Matsuda which provides a good approximation of measurements of whole-body insulin sensitivity obtained by the glucose clamp technique¹⁴:

$$\text{ISI(MATSUDA)} = \frac{10000}{\sqrt{G0 \times I0 \times G_{\text{mean}} \times I_{\text{mean}}}}$$

ISI is the insulin sensitivity index, G0 the fasting plasma glucose (mg/dL), I0 the fasting plasma insulin (mIU/L), Gmean

the mean plasma glucose during OGTT (mg/dL), and Imean is the mean plasma insulin during OGTT (mIU/L).

Insulinogenic index (IGI), a measure of early phase insulin secretion, defined as the ratio of the increment of insulin to that of plasma glucose 30 minutes after a glucose load, was calculated with the formula:

$$IGI = \frac{\Delta Insulin_{0-30min}}{\Delta Glucose_{0-30min}}$$

Oral disposition index (ODI), a measure of β -cell function integrated with insulin sensitivity, was calculated with the formula:

$$ODI = IGI \times ISI$$

STATISTICAL ANALYSIS

Data are expressed as mean \pm standard deviation (SD), median (25th–75th percentile), or number (percentage) as appropriate. Continuous variables that were not normally distributed were ln-transformed before analysis. Paired samples Student's *t* test was used to compare means. The Pearson product-moment correlation coefficient was used to evaluate correlation between variables.

A *P*-value < 0.05 was considered statistically significant. All tests were two-tailed. The Statistics Package for Social Sciences (SPSS for Windows, version 17.0, SPSS Inc., Chicago, IL) was used for all analyses. GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA) was used to create the graphs.

RESULTS

Baseline Characteristics of the Study Population

Fifteen (8 males, 7 females) patients were recruited and included in the analysis. Baseline characteristics of the study population are summarized in Table 1.

The mean age was 52.7 \pm 10.5 years. The mean disease duration was 52.1 \pm 38 months. All patients were under stable treatment with methotrexate (range 15–20 mg/week), and only 4 patients were concurrently treated with hydroxychloroquine (200–400 mg/daily). On average, patients tended to be overweight (mean BMI: 26.5 \pm 5.9 kg/m²) with a trend toward a visceral distribution of fat (mean waist circumference 99.3 \pm 14.7 cm). Mean systolic blood pressure was 124.3 \pm 12.8 mm Hg while mean diastolic blood pressure was 77.5 \pm 10.1 mm Hg. Five (33%) patients had a previous diagnosis of high blood pressure. Four (26.7%) patients satisfied National Cholesterol Education Program-Adult Treatment Panel (ATPIII) criteria³³ for the diagnosis of MS.

Effect of Abatacept on Disease Activity

All patients were treated with i.v. abatacept with appropriate dosage for weight range, as suggested by manufacturer.²⁹ As expected, tender joint count (10 [6–14] versus 1 [0–5], *P* = 0.003), global health-visual analogic scale (79.3 \pm 14.8 mm versus 34.0 \pm 26.7 mm, *P* < 0.001), ESR (18.9 \pm 12.2 mm/h versus 8.9 \pm 6.0 mm/h, *P* = 0.006), hs-CRP (4.2 [2.2–16.0] mg/L versus 3.0 [0.6–6.8] mg/L, *P* = 0.02), and DAS28-CRP (4.9 \pm 0.8 versus 2.7 \pm 1.0, *P* < 0.001), but not swollen joint count, significantly improved after 6 months of the treatment with abatacept (Table 2). Also anticyclic citrullinated peptide antibodies, but not RF, were significantly reduced after treatment (1120 [94–2922] versus 324 [44.5–1056], *P* = 0.01). Ten

TABLE 1. General Characteristics of the Study Population

Patients	All Patients (n = 15)
Males n, %	8 (53.3)
Age, years	52.7 \pm 10.5
Disease duration, months	52.1 \pm 38.3
Rheumatoid factor (IU/mL)	48.6 (36.6–68.0)
% positive	93.3
ACPA (IU/mL) % positive	1120 (94–2922) 86.7
High blood pressure n, %	5 (33.3)
Metabolic syndrome n, %	4 (26.7)
Weight, kg	72.0 (58.0–80.4)
Height, m	1.66 \pm 0.10
BMI, kg/m ²	26.5 \pm 5.9
Waist circumference, cm	99.3 \pm 14.7
sBP, mm Hg	124.3 \pm 12.8
dBP, mm Hg	77.5 \pm 10.1
Current treatments	
Methotrexate n, %	15 (100)
Hydroxychloroquine n, %	4 (26.7)
ACEi or ARBs n, %	5 (33.3)
β -Blockers n, %	1 (6.7)
Other blood pressure lowering drugs n, %	2 (13.3)
ASA n, %	0 (0)
Statins n, %	2 (13.3)

ACPA = anticitrullinated protein antibodies; ACEi, angiotensin-converting enzyme (ACE) inhibitors; ARBs = angiotensin II receptor blockers; ASA = acetylsalicylic acid; BMI = body mass index; dBP = diastolic blood pressure; sBP = systolic blood pressure.

patients (66.6%) achieved a good response according to EULAR response criteria,³¹ 4 patients (26.7%) achieved a moderate response and only 1 patient (6.7%) was classified as nonresponder.

Effect of Abatacept on Measures of Adiposity and Blood Pressure

Given the expected ability of abatacept to improve disease activity, and to evaluate a possible influence of modification of

TABLE 2. Measures of Inflammation and Disease Activity Before and After Treatment

	Time 0	Time 6 mo	<i>P</i> value
TJC (n)	10 (6–14)	1 (0–5)	0.003
SJC (n)	1 (0–4)	0 (0–1)	0.10
GH-VAS, mm	79.3 \pm 14.8	34.0 \pm 26.7	<0.001
ESR, mm/h	18.9 \pm 12.2	8.9 \pm 6.0	0.006
hs-CRP, mg/L	4.2 (2.2–16.0)	3.0 (0.6–6.8)	0.02
DAS28-CRP	4.9 \pm 0.8	2.7 \pm 1.0	<0.001
RF, IU/mL	48.6 (36.6–68)	18.7 (11.9–68)	0.26
ACPA, IU/mL	1120 (94–2922)	324 (44.5–1056)	0.01

ACPA = anticyclic citrullinated peptide antibodies; DAS28-CRP = disease activity score 28 joints; ESR = erythrocyte sedimentation rate; GH-VAS = global health-visual analogic scale; hs-CRP = high sensitivity C-reactive protein; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.

insulin sensitivity related to body weight and blood pressure, we next evaluated the effect of this molecule on measures of adiposity and blood pressure. Body weight (72 [58.0–80.4] kg versus 75 [62.5–88.2] kg, $P=0.07$), BMI (26.5 ± 5.9 kg/m² versus 27.8 ± 5.6 kg/m², $P=0.08$), waist circumference (99.3 ± 14.7 cm versus 97.1 ± 12.0 cm $P=0.21$), systolic (124.3 ± 12.8 mm Hg versus 121.3 ± 9.9 mm Hg, $P=0.45$), and diastolic (77.5 ± 10.1 mm Hg versus 75.8 ± 8.3 mm Hg, $P=0.54$); blood pressure did not change significantly during the observation period (Table 3).

Effect of Abatacept on Insulin Sensitivity

We next aimed to investigate if insulin sensitivity is affected by abatacept. To evaluate insulin sensitivity before and after 6 months of the treatment, we performed an OGTT in all patients and calculated Matsuda ISI, a surrogate measure of insulin sensitivity. ISI significantly increased after the treatment with abatacept from 3.7 ± 2.6 to 5.0 ± 3.2 ($P=0.003$) with a mean difference of 1.23 (Figure 1). Similar results were obtained after removing patients under treatment with hydroxychloroquine (3.0 ± 2.2 versus 4.1 ± 2.4, $P=0.01$) or patients with high blood pressure (4.4 ± 2.9 versus 5.6 ± 3.6, $P=0.02$). Single time-point analysis revealed a significant reduction in fasting glucose (93 ± 11 mg/dL versus 86 ± 10 mg/dL, $P=0.03$), glucose at 30 minutes (168 ± 37 mg/dL versus 146 ± 33 mg/dL, $P=0.009$), glucose at 90 minutes (158 ± 53 mg/dL versus 136 ± 49 mg/dL, $P=0.005$), insulin at 30 minutes (103.0 ± 66.4 mIU/L versus 67.9 ± 35.7 mIU/L, $P=0.005$), insulin at 60 minutes (125.0 ± 66.4 mIU/L versus 103.0 ± 64.6 mIU/L, $P=0.02$), and insulin at 90 minutes (136.1 ± 86.9 mIU/L versus 97.8 ± 70.6 mIU/L, $P=0.01$). No significant differences were found in glucose at 60 minutes, glucose at 120 minutes, fasting insulin and insulin at 120 minutes (Table 4). Taken together these data resulted in a reduction of both glucose (303.9 ± 73.4 mg/dL min versus 269.2 ± 69.5 mg/dL min, $P=0.009$) and insulin (208.4 ± 119.7 mg/dL min versus 158.0 ± 95.3 mg/dL min, $P=0.01$) AUCs, as showed in Figure 2.

According to this finding also A1c significantly improved (5.5 ± 0.4% versus 5.3 ± 0.3%, $P=0.04$) after 6 months of treatment with abatacept.

No significant differences after treatment with abatacept were found for measures of β-cell function IGI (1.11 ± 1.19 versus 1.32 ± 0.82, $P=0.77$) and oral disposition index (2.0 ± 5.4 versus 6.0 ± 6.0, $P=0.25$).

Determinants of Insulin Sensitivity

In univariate correlational analysis, ISI (Matsuda) showed a strong inverse correlation with both measures of adiposity and

TABLE 3. Measures of Adiposity and Blood Pressure Before and After Treatment

	Time 0	Time 6 mo	P value
Weight, kg	72.0 (58.0–80.4)	75.0 (62.5–88.2)	0.07
BMI, kg/m ²	26.5 ± 5.9	27.8 ± 5.6	0.08
Waist, cm	99.3 ± 14.7	97.1 ± 12.0	0.21
Sbp, mm Hg	124.3 ± 12.8	121.3 ± 9.9	0.45
dBp, mm Hg	77.5 ± 10.1	75.8 ± 8.3	0.54

BMI = body mass index, dBp = diastolic blood pressure, sBP = systolic blood pressure.

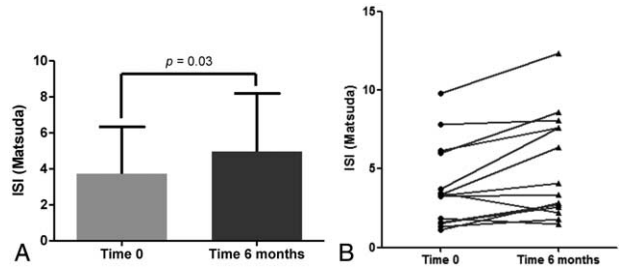


FIGURE 1. The effect of abatacept on insulin sensitivity. (A) Mean values of ISI for the whole population before and after 6 months of treatment with abatacept. (B) ISI values in individual patients before and after treatment. ISI = insulin sensitivity index.

inflammation at time 0. In particular, ISI correlated with BMI ($R=-0.71$, $P=0.003$), waist circumference ($R=-0.81$, $P<0.001$), uric acid ($R=-0.62$, $P=0.01$), LDL cholesterol ($R=-0.63$, $P=0.02$), ESR ($R=-0.72$, $P=0.003$), and ln-CRP ($R=-0.72$, $P=0.002$). At the 6 months time-point, the correlation was maintained for all metabolic parameters (BMI: $R=-0.57$, $P=0.02$; waist circumference: $R=-0.72$, $P=0.002$; and uric acid: $R=-0.55$, $P=0.03$) and for ESR ($R=-0.54$, $P=0.03$) but not for hs-CRP ($R=-0.33$, $P=0.22$). However, ESR, but not CRP, showed a strong collinearity with BMI ($R=0.54$, $P=0.03$).

Effect of Abatacept on Other Metabolic Parameters

Finally, we aimed to investigate the effect of abatacept on other metabolic parameters. During the study period, we

TABLE 4. Glucose and Insulin Values During Oral Glucose Tolerance Test and Measures of Insulin Sensitivity Before and After Treatment

	Time 0	Time 6 mo	P value
Fasting glucose, mg/dL	93 ± 11	86 ± 10	0.03
30-min glucose, mg/dL	168 ± 37	146 ± 33	0.009
60-min glucose, mg/dL	172 ± 51	154 ± 50	0.14
90-min glucose, mg/dL	158 ± 53	136 ± 49	0.005
120-min glucose, mg/dL	125 ± 45	117 ± 25	0.51
Fasting insulin, mIU/L	11.2 ± 6.5	10.3 ± 5.0	0.45
30-min insulin, mIU/L	103.0 ± 66.4	67.9 ± 35.7	0.005
60-min insulin, mIU/L	125.0 ± 66.4	103.0 ± 64.6	0.02
90-min insulin, mIU/L	136.1 ± 86.9	97.8 ± 70.6	0.01
120-min insulin, mIU/L	94.2 ± 83.0	84.4 ± 69.4	0.59
Mean glucose, mg/dL	143.3 ± 33.7	128.0 ± 30.1	0.01
Mean insulin, mIU/L	93.9 ± 55.9	72.7 ± 44.8	0.03
Glucose AUC, mg/dL min	303.9 ± 73.4	269.2 ± 69.5	0.009
Insulin AUC, (mg/dL min)	208.4 ± 119.7	158.0 ± 95.3	0.01
ISI (Matsuda)	3.7 ± 2.6	5.0 ± 3.2	0.003
IGI	1.11 ± 1.19	1.32 ± 0.82	0.77
ODI	2.0 ± 5.4	6.0 ± 6.0	0.25
A1c, %	5.5 ± 0.4	5.3 ± 0.3	0.04

A1c = glycated hemoglobin, AUC = area under the curve, IGI = insulinogenic index, ISI (Matsuda) = Matsuda insulin sensitivity index, ODI = oral disposition index.

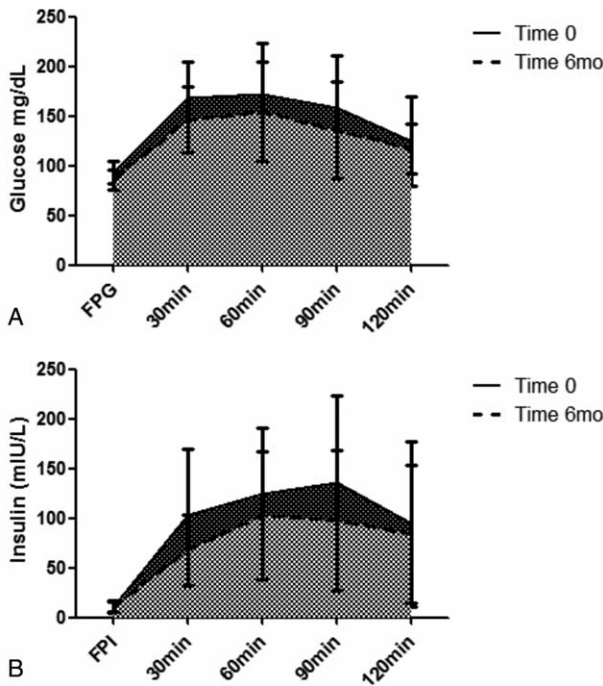


FIGURE 2. The effect of abatacept on glucose and insulin area under the curve (AUC) in the whole group. (A) Effect of abatacept on glucose area under the curve (AUC) in the whole group. (B) Effect of abatacept on insulin AUC in the whole group.

observed a significant increase in ApoA1 (1.46 ± 0.32 g/L versus 1.75 ± 0.35 g/L, $P = 0.01$) and ApoB (0.82 ± 0.21 g/L versus 0.93 ± 0.22 g/L, $P = 0.02$), while no significant differences were observed for creatinine, uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, alanine aminotransferase, and aspartate aminotransferase (Table 5).

DISCUSSION

In this preliminary study, we demonstrate for the first time that abatacept, a novel molecule approved for treatment of RA, improves whole body insulin sensitivity in RA patients with

moderate to active disease despite treatment with methotrexate. Whole-body insulin sensitivity was estimated with the surrogate measure ISI (Matsuda),¹⁴ calculated from glucose and insulin values during OGTT. In several studies involving different populations of patients, ISI correlated strongly with the glucose clamp technique, the gold standard for determining insulin sensitivity in vivo but still difficult to apply in clinical setting because of its time expensive procedure. In our population, this result was maintained also after removal of patients under current treatment with hydroxychloroquine, a medication that showed insulin-sensitizing properties.

According to our data, the observed improvement in insulin sensitivity was not related to a significant loss of weight or redistribution of body fat. In addition, before treatment with abatacept, ISI was strongly correlated with inflammatory parameters and this correlation was lost after treatment, suggesting a possible relation between disruption of inflammation and improvement in insulin sensitivity.

Preclinical evidences help us to hypothesize the possible mechanisms behind this novel effect of abatacept. Immune cells, in particular macrophages and T cells are nowadays recognized as important players in the pathogenesis of adipose tissue inflammation and, consequently, IR.³⁴

Preliminary studies showed that macrophages are recruited in adipose tissue of obese mice³⁵ and contribute to inflammation by the local production of inflammatory mediators.³⁶ The role of macrophages as terminal effectors of inflammation-related IR have been recently emphasized by the evidence that pioglitazone, an insulin-sensitizing agent used in the treatment of diabetes, reduces adipose tissue infiltrating macrophages, and this reduction is accompanied by an improvement of IR.³⁷

Subsequently, Kintscher et al³⁸ and Nishimura et al³⁹ demonstrated that T cells infiltration of adipose tissue precedes the accumulation of macrophages. Moreover, reduction of T cells with anti-CD3 antibodies seems to reverse IR.⁴⁰ Recently, Khan et al showed that mice lacking $\alpha\beta$ T cells are protected against obesity-induced hyperglycemia and IR.⁴¹

Regulatory T cells (Treg), a distinct CD4⁺ lymphocytes population characterized by the expression of FoxP3, represent a distinct lineage with the ability to suppress autoimmune and other pathological immune responses. Tregs are abundant in visceral fat of normal mice, while they are significantly reduced in obesity.⁴² Conversely, adoptive transfer⁴³ or experimental

TABLE 5. Other Metabolic Parameters Before and After Treatment with Abatacept

	Time 0	Time 6 mo	P value
Total cholesterol, mg/dL	174.0 (145.5–195.3)	169.0 (163.0–217.0)	0.16
HDL-cholesterol, mg/dL	57.7 ± 16.3	59.3 ± 17.7	0.45
LDL-cholesterol, mg/dL	106.7 ± 27.6	121.5 ± 36.0	0.22
Triglycerides, mg/dL	79.0 (54.0–103.0)	91.0 (54.0–120.0)	0.18
TC/HDL	3.15 ± 1.36	3.45 ± 1.14	0.23
ApoA1, g/L	1.46 ± 0.32	1.75 ± 0.35	0.01
ApoB, g/L	0.82 ± 0.21	0.93 ± 0.22	0.02
ApoB/ApoA1	0.60 ± 0.24	0.55 ± 0.18	0.25
Creatinine, mg/dL	0.71 ± 0.14	0.71 ± 0.17	0.79
Uric acid, mg/dL	5.17 ± 1.45	4.73 ± 1.20	0.06
ALT, UI/L	19.0 (14.0–24.0)	21.0 (11.0–32.0)	0.47
AST, UI/L	19.2 ± 6.5	22.9 ± 10.6	0.09

ALT = alanine aminotransferase, ApoA1 = apolipoprotein A, ApoB = apolipoprotein B, AST = aspartate aminotransferase, TC/HDL = total cholesterol/HDL cholesterol ratio.

induction⁴⁴ of Tregs resulted in a significant improvement in IR in mouse models of obesity.

In 2010, Ko et al⁴⁵ demonstrated that CTLA-Ig increases the number of Tregs in joints and spleen of collagen-induced arthritis mice, mainly through the modification of dendritic cells. In addition, CTLA-Ig treatment does not affect the stability of Tregs,⁴⁶ but it rather seems to increase their proliferation and suppressive activity.⁴⁷ In RA patients, the consequences of CTLA-Ig treatment on Tregs are still poorly understood.⁴⁸ However, Álvarez-Quiroga et al⁴⁹ demonstrated that abatacept seems to enhance Tregs function although conditioning a reduction in number. Recently, Vogel et al⁴⁷ demonstrated that blocking the costimulation resulted in an altered balance between effector T cells and Tregs, in favor of Treg activity.

Fujii et al⁵⁰ recently demonstrated that abatacept improved IR in a mouse model of diet-induced obesity, mainly through polarization of adipose tissue macrophages from the proinflammatory M1 to the antiinflammatory M2 phenotype.

Taken together, these evidences support the hypothesis that inhibition of T cells costimulation could improve insulin sensitivity by at least 2 mechanisms: the reduction of effector T cells in adipose tissue and/or the enhancement of Treg activity. Therefore, from a pathophysiological point of view, our work provides additional evidences supporting the hypothesis of an important role of T cells in IR.

As collateral data, we found that abatacept treatment increases ApoA1, ApoB. Similar data have been reported with other biologics with different mechanisms of action, such as infliximab,⁵¹ tocilizumab,⁵² and in patients treated with conventional DMARDs.⁵³ In our study, however, there were no statistically significant differences in total cholesterol/HDL ratio and ApoB/ApoA1 ratio, both representing a more accurate measure of cardiovascular risk when compared with single serum lipid determinations.^{54,55} Therefore, the clinical significance of this observation appears controversial, because on the other hand there are preclinical evidences supporting a positive effect of blocking costimulation in the development and progression of atherosclerosis;⁵⁶ these divergent results could reflect the complex role of T cells, and Treg in particular, in lipoprotein metabolism as suggested by recent evidences.⁵⁷

Major limitations of our study include the small sample size, the lack of a control group and a use of a surrogate, although largely validated, measure of insulin sensitivity. Another possible limitation is the elevated prevalence of high blood pressure in the study population. High blood pressure is strictly correlated with insulin sensitivity, and these 2 conditions share common pathophysiological mechanisms such as chronic adrenergic stimulation.^{25,58–60} However, the low number of patients in our study made difficult to perform a sub-analysis to evaluate the possible influence of blood pressure on the main outcome.

In conclusion, our study, although limited by the observational design, the low number of patients, and the lack of a control group, provides preliminary evidences for a potential insulin-sensitizing effect of abatacept. These findings, together with other emerging effects of abatacept supporting a favorable cardiovascular profile,^{61,62} open new scenarios in the future of this molecule. However, our data need to be confirmed by more adequate studies, including a control group and direct measurements of insulin sensitivity with the glucose clamp technique, bypassing the limitations of surrogate measures in the context of longitudinal studies.⁶³ Our finding, if confirmed, could improve the management of comorbidity in RA patients.

Cardiometabolic risk management, according to the EULAR recommendations, should be one of the biggest efforts for clinicians dealing with RA patients.

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