Role of adiponectin in non-diabetic patients with rheumatoid arthritis undergoing anti-IL-6 therapy

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Abstract

Objective

Adiponectin is an adipokine that plays a relevant role in the development of metabolic syndrome (MetS), a complication that increases the risk of cardiovascular (CV) disease in patients with rheumatoid arthritis (RA). Accordingly, we assessed for the first time the short-term effect of anti-IL-6 receptor tocilizumab (TCZ) administration on adiponectin serum levels in RA patients and explored the potential association of adiponectin levels with MetS features, other CV risk factors and demographic and clinical characteristics of these patients.

Methods

Adiponectin serum levels were evaluated in 50 non-diabetic RA patients, undergoing TCZ treatment, immediately prior to (pre-infusion) and 60 minutes after the end of a TCZ intravenous infusion (post-infusion).

Results

No significant differences in adiponectin levels pre- and post-TCZ infusion were found in RA patients ($p=0.69$). Patients with obesity exhibited decreased basal levels of adiponectin with respect to those non-obese ($p=0.03$). Additionally, a negative association of adiponectin basal levels with body mass index, insulin, insulin/glucose index, C-peptide and leptin levels ($p<0.01$; $p=0.02$; $p=0.03$; $p=0.03$ and $p=0.01$, respectively), as well as a positive correlation with HDL-cholesterol levels ($p<0.001$) was seen.

Conclusion

Our results support the claim that low adiponectin may contribute to the development of MetS and, consequently, CV disease in RA. Anti-IL-6 therapy does not seem to exert a short-term effect on adiponectin levels.

Key words

rheumatoid arthritis, metabolic syndrome, cardiovascular disease, adiponectin, anti-IL-6 receptor tocilizumab.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with an increased incidence of metabolic syndrome (MetS) (1-4). MetS represents a cluster of metabolic abnormalities and cardiovascular (CV) complications that directly increase the risk of CV morbidity and mortality in patients with RA (2, 5-7). Thus, MetS has been described as a potential link between CV and arthritic diseases (1, 5, 7, 8).

Adipokines are pleiotropic molecules that contribute to the pathogenesis of MetS by playing physiological roles in processes such as energy expenditure, appetite, coagulation and inflammation (5, 8). Among the different adipokines, adiponectin and leptin have been identified as important factors involved in the interaction between metabolism and rheumatic disorders such as RA (7, 9). In particular, adiponectin is the most abundant adipokine secreted primarily by the adipose tissue. This molecule exerts anti-inflammatory and cardioprotective effects, being involved in the insulin sensitivity and in the protection against the development of diseases associated with obesity (7, 8, 10-12). On the contrary, leptin has been established as a pro-inflammatory adipokine with a negative impact on CV function (7, 12, 13).

Given the contribution of adiponectin and leptin on the inflammatory response in RA, the study of the influence of biologic therapies on the levels of these adipokines is of potential interest (1, 6-9, 11, 13-16). Tocilizumab (TCZ), a humanised anti-human IL-6 receptor monoclonal antibody, has been effectively used in the treatment of RA (17). In this sense, we recently disclosed a short-term effect of TCZ therapy on leptin serum levels in RA patients (18). Accordingly, we hypothesized that anti-IL-6 therapy may also have a short-term effect on adiponectin levels, exerting a beneficial effect on the MetS in RA.

In the present study we aimed to assess for the first time the short-term effect of TCZ on circulating adiponectin serum levels in 50 non-diabetic patients with RA that were on periodical treatment with this biologic agent. We also explored the potential association of adiponectin levels with MetS features and other CV risk factors, as well as with the demographic and clinical characteristics of these patients.

Patients and methods

Patient population

A series of 50 consecutive non-diabetic patients diagnosed with RA according to the 1987 and 2010 American College of Rheumatology classification criteria (19, 20) and undergoing periodic treatment with the anti-IL-6 monoclonal antibody-TCZ were included in this study. The main characteristics of this series of patients have previously been described (21). Briefly, there was a predominance of women (80%) with a mean duration of the disease of 12.6 years. Almost 70% were rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies positive. The mean disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR) at the time of assessment was 3.2.

These patients were on periodical treatment with TCZ (RoActemra®, Roche Laboratories, Spain), which was administered intravenously at variable doses ranging between 4 and 8 mg/kg every 4–6 weeks. These series of patients included long-standing RA patients. In all the cases, the monoclonal antibody TCZ treatment was started because of active disease. All the patients had failed at methotrexate and, in most of the cases, at other biologic agents. These patients were recruited from the Rheumatology outpatient clinics of Hospital de La Princesa (Madrid, Spain) and Hospital de Sierrallana (Cantabria, Spain).

Patients with diabetes, fasting plasma glucose levels >125 mg/dL or currently taking anti-diabetic oral drugs were excluded. In addition, patients with 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.

The study protocol was in accordance with the principles of the Declaration of Helsinki and was approved by the local institutional ethics committee of every participant center. All participants gave their written informed consent to participate in this study before their inclusion. This study has not been supported by any pharmaceutical company.

Study protocol

A commercial immunoassay kit was used to measure human adiponectin serum levels (Human Adiponectin ELISA Kit, EZHADP-61K, Linco Research Inc., USA).

The impact of TCZ on adiponectin were evaluated by comparing the serum levels of this adipokine before and after therapy administration in each patient. In all the cases, TCZ was given as an intravenous infusion in a saline solution over 60 minutes. The first sample was taken immediately prior to the TCZ infusion (pre-infusion), and the second sample 60 minutes after finishing TCZ infusion (post-infusion). Simultaneously, vital signs were also registered before and after TCZ administration. All the measurements were made in the fasting state.

Routine laboratory parameters and leptin serum levels assessed from blood samples taken prior to TCZ infusion as previously described (18, 21), were used to analyse the potential association of basal adiponectin levels with MetS features and other CV risk factors.

Statistical analyses

Results were reported as mean ± standard deviation (SD). For the comparison of adiponectin serum levels before and after TCZ infusion, paired Student's t-test was used. Relationship of adiponectin levels prior to TCZ (basal) with selected continuous and categorical variables was performed adjusting by age at the time of the study, sex and classic CV risk factors (dyslipidaemia, obesity and arterial hypertension) via estimation of the Pearson's partial correlation coefficient (r) and lineal regression, respectively. Statistically significant differences were considered at $p<0.05$. Statistical analysis was performed using the software STATA 12/SE (StataCorp, College Station, TX, USA).

Results

Changes in adiponectin concentrations upon TCZ therapy

No short-term effect of TCZ administration on circulating adiponectin levels was disclosed. In particular, patients with RA did not show differences in adiponectin levels observed prior to (time 0) and after (time 60 minutes) TCZ infusion (mean±SD: 23014.45±19583.67 ng/mL *vs*. 22346.08±17844.16 ng/mL, respectively, $p=0.69$) (Fig. 1).

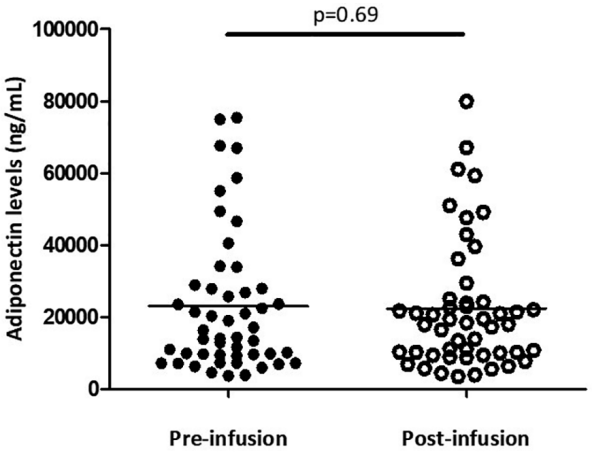

Fig. 1. Basal (time 0) and post-TCZ infusion (time 60 minutes) adiponectin levels in RA patients. Horizontal bars indicate mean value of each study group.

Table I. Differences in adiponectin basal levels according to categorical variables, adjusting for age at the time of the study, sex and classic cardiovascular risk factors.

Variable	Category (n)	Adiponectin (ng/mL)	
		Mean ± SD	*p*
Sex	Men (8)	10766.98 ± 7246.95	0.06
	Women (42)	25347.30 ± 20360.35	
RF antibodies	Yes (34)	24060.91 ± 21843.00	0.49
	No (15)	20319.49 ± 14337.76	
Anti-CCP antibodies	Yes (24)	22920.82 ± 20086.80	0.55
	No (11)	18312.03 ± 14252.11	
Obesity	Yes (10)	**11539.03 ± 9094.92**	**0.03**
	No (40)	**25884.55 ± 20506.75**	
Arterial hypertension	Yes (22)	25280.49 ± 22353.63	0.56
	No (28)	21233.98 ± 17317.71	
Dyslipidemia	Yes (14)	23971.77 ± 21592.89	0.85
	No (36)	22642.15 ± 19058.85	

SD: standard deviation; RF: rheumatoid factor; anti-CCP: Anti-cyclic citrullinated peptide. Significant results are highlighted in bold.

Relationship of adiponectin concentration with MetS features and other CV risk factors

Patients with obesity exhibited decreased basal levels of adiponectin with respect to those non-obese (11539.03 ± 9094.92 ng/mL *vs*. 25884.55 ± 20506.75 ng/mL, respectively, $p=0.03$) (Table I). Accordingly, a significant negative correlation between adiponectin basal levels and BMI was found (r=-0.45; $p<0.01$) (Table II). Regarding insulin metabolism, we noticed a negative association of adiponectin basal levels with insulin, insulin/glucose index and C-peptide (r=-0.33, $p=0.02$; r=-0.32, $p=0.03$; r=-0.32, $p=0.03$, respectively) (Table II). Moreover, a positive correlation was disclosed between basal levels of adiponectin and high-density lipoprotein (HDL)-cholesterol levels (r=0.51; $p<0.001$) (Table II). In relation to leptin, we found that its basal levels were negatively correlated with adiponectin basal levels (r= -0.36; $p=0.01$) (Table II).

No significant associations were observed between adiponectin basal concentrations and other features of MetS or other CV risk factors (Tables I-II).

Relationship of adiponectin concentration with demographic and clinical characteristics

No significant associations were found between adiponectin basal levels and demographic and clinical characteristics, including RF and anti-CCP antibodies status and disease activity parameters (Tables I-II).

Discussion

Adipokines may provide a potential link between adiposity, MetS and inflammation, contributing to explain the enhanced CV risk in patients with RA (7, 8). Thus, the variability of adipokine levels and other molecules implicated in lipid metabolism, such as PCSK9, caused by the effect of biologic therapies in RA patients has deserved great attention in the last years (1, 6-9, 11, 13-16, 22). Accordingly, we recently disclosed a short-term effect of TCZ therapy on leptin serum levels in RA patients (18). However, in relation to adiponectin, an adipokine that seems to have a protective role in MetS and have been evidenced as a modulator of RA pathophysiology (5), only the long-term impact of TCZ on this adipokine has been evaluated in RA patients (1, 6, 8, 9, 16). Hence, the purpose of this study was to assess for the first time the short-term effect of TCZ administration on adiponectin serum levels in RA patients as well as to explore the potential association of adiponectin levels with MetS features, other CV risk factors and demographic and clinical characteristics of these patients.

Our results revealed that IL-6 receptor blockade using TCZ did not change the circulating levels of adiponectin in the short-term in patients with RA. The same results in the short-term were found in a former study of our group in which RA patients received anti-TNF treatment, another biologic therapy used for RA (15). In keeping with our data, previous reports showed that adiponectin levels were also unaltered when the long-term effect of TCZ were assessed in RA patients (6, 16). In this sense, although some authors have shown a significant influence of IL-6 inhibition on adiponectin levels (1, 8, 9), our study suggests that the blockade of IL-6 signaling does not seem to exert a short-term effect on adiponectin levels. It is conceivable that changes of adiponectin levels following IL-6 blockade could depend on the degree of severity of MetS present at the onset of TCZ therapy. In this respect, our series of non-diabetic RA patients were already undergoing TCZ therapy. In all the cases, patients had been treated with methotrexate and in many cases had also received biologics. Accordingly, it is possible that this active management of the disease before the onset of anti-IL-6 therapy might have reduced the effect of TCZ infusions on adiponectin levels. On the other hand, taking into consideration that we measured the potential change of adiponectin only one hour after the end of the TCZ intravenous infusion, it is also plausible to think that this may be a small period of time to identify changes in this adipokine.

It is well-known that adiponectin plays a relevant role in the development of MetS (5, 7, 8, 11). In this context, we observed that basal adiponectin serum levels were decreased in obese RA patients compared to non-obese RA patients. This relationship between adiponectin and obesity was further evidenced by a significant negative correlation of this adipokine with BMI. These data confirm previous reports that showed that adiponectin levels are inversely proportional to obesity and fat mass (5, 7, 9-12, 14). Furthermore, adiponectin has been involved in the insulin metabolism playing a crucial role in glucose and lipid homeostasis (5). This role of adiponectin was supported by the negative association of adiponectin levels with insulin, insulin/glucose index and C-peptide found in our cohort of non-diabetic RA patients. Besides, in keeping with other studies, we disclosed a positive correlation of HDL-cholesterol levels with adiponectin concentrations (5, 12). Moreover, in accordance with the opposite metabolic effects of leptin and adiponectin, we found a negative association between these adipokines (14, 23). Overall, these findings indicate that adiponectin is downregulated in individuals with MetS, further validating its cardioprotective role. Accordingly, the determination of adiponectin levels in the clinical practice may be a good biomarker of MetS, improving the

Table II. Partial correlation of adiponectin basal levels with selected continuous variables, adjusting for age at the time of the study, sex and classic cardiovascular risk factors.

Variable	Adiponectin	
	r	*p*
Age at the onset of symptoms	-0.17	0.26
Disease duration	0.16	0.29
Disease Activity		
DAS28-ESR	0.09	0.55
DAS28-CRP	0.07	0.66
Swollen Joints	0.03	0.82
Tender Joints	0.04	0.79
VAS patient	0.06	0.70
CRP	-0.11	0.45
ESR	-0.07	0.65
Metabolic syndrome		
BMI	**-0.45**	**<0.01**
Glucose	-0.03	0.84
Insulin	**-0.33**	**0.02**
Insulin/Glucose Index	**-0.32**	**0.03**
HOMA-IR	-0.23	0.12
QUICKI	0.23	0.12
Total cholesterol	0.27	0.06
HDL-cholesterol	**0.51**	**<0.001**
LDL-cholesterol	0.01	0.95
Triglycerides	-0.22	0.15
C-peptide	-0.32	**0.03**
Systolic blood pressure	-0.10	0.53
Diastolic blood pressure	-0.003	0.98
Leptin	**-0.36**	**0.01**

DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index; HDL: high-density lipoprotein; LDL: low-density lipoprotein. Significant results are highlighted in bold.

identification of RA patients with MetS and higher risk of CV disease.

In conclusion, our results support that low adiponectin levels may contribute to the development of MetS and, consequently, CV disease in RA. In addition, anti-IL-6 therapy does not seem to exert a short-term effect on adiponectin levels.

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