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Inflammation-lowering effects of oral antidiabetic drugs in rheumatoid arthritis

Iulia Roman[2], Maria Magdalena Negru[1,2], Florian Berghea[1,2], Madalina Duna[2], Cristina Stoian[2], Denisa Predeteanu[1,2], Ruxandra Ionescu[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Department of Internal Medicine and Rheumatology, "Sf. Maria" Clinical Hospital, Bucharest, Romania

ABSTRACT

Objective. The primary aim of this study is to underline the inflammation-lowering effect of oral antidiabetic drugs, namely the CRP, ESR and DAS28 levels. The secondary aim was to show that these effects are dependent on the dose of the antidiabetic drug.
Methods. The study has an observational, case-control design. The information was gathered from the case reports of the patients that were admitted in Sf. Maria Clinical Hospital in Bucharest, beginning with 2010 and until May 2016. It included a case group of 20 subjects and a control group of 20 subjects who were followed approximately 3 years from the diagnosis of RA.
Results. There were no significant group differences at baseline. During the follow-up, the medians of DAS28, CRP and ESR were significantly lower in the group treated with oral glucose lowering agents ($p<0.005$). Secondly, the presence of metformin both as monotherapy and in combination with other antidiabetic drugs was associated with a statistically significant decrease in the medians of the three mentioned variables ($p<0.05$). The metformin-dose can predict the value of CRP ($p=0.005$), accounting for 18.9% of the variation of CRP. Moreover, there is a negative correlation between CRP level and metformin, $r=-0.434$, $p=0.003$. This negative correlation was also seen between metformin and CRP value ($p=0.027$), when metformin was used in monotherapy.
Conclusion. The main insights achieved in this study relate to the ability of metformin to significantly lower both DAS28 and CRP level in patients with RA and T2DM, when compared to those that are affected only by RA. An element that needs further study is if these benefits can also extend to RA patients without T2DM, but with impaired glucose tolerance or important cardiovascular risk factors.

Keywords: Metformin, oral antidiabetic drugs, rheumatoid arthritis, inflammation

INTRODUCTION

Rheumatoid arthritis is defined as a chronic inflammatory disease, characterised by joint swelling, tenderness and synovial joint destruction, associated with a variety of systemic autoimmune manifestations, all adding to a premature mortality, functional disability and lower quality of life (1). The immune mechanisms that lead to RA are complex and have repercussions not only at the joint level, but also on metabolic processes and the endothelial function.

The pathogenesis of RA can be seen as a multistep process, transiting the following stages (2): initiation of autoimmunity, amplification of autoimmune mechanisms, chronic inflammation and tissular destruction. The first step can occur as a result of three possible mechanisms: genetic predisposition, activation of innate immunity or loss of self-tolerance. The presence of autoantibodies can be detected starting with this phase and their serum concentration begins to rise in the second phase. These two phases pertain to the subclinical stage of the disease, which is characterised by the absence of symptoms and detection of serum autoantibodies and inflammatory markers in the second phase. (3)

The plethora of cytokines present in the patients' serum and cellular inflammatory processes that are activated during the first two phases can also have metabolic effects (4). Evidence for this statement resides in the fact that the changes in lipid and glucose profile are more prevalent in RA patients and are most significant in the early stage of the disease (5,6), these alterations being attenuated during remissive treatment (7). However, drugs that modulate lipid levels, like statins and antidiabetic drugs that act on insulin sensitivity can also lower disease activity, suggesting a pathophysiological interplay between different metabolic pathways and RA.

Corresponding author:
Iulia Roman
E-mail: roman.i.iulia@gmail.com

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This systemic inflammatory status has not only metabolic, but also cardiovascular repercussions, namely by accelerating the atherosclerosis process. Patients with RA have a higher cardiovascular (CV) risk than the rest of the population, this risk being higher in patients (with early rheumatoid arthritis) (8). Moreover, RA is considered as an independent CV risk factor (9) and studies have shown that the initiation of remissive therapy for RA decreases the rate of CV events and the progression of atherosclerotic plaques, emphasizing the degree of similarity between the pathogenesis of these two affections.

As highlighted before, several drugs that target specific CV risk factors such as statins and insulin sensitizers, also have an effect on the disease activity of patients with RA and the levels of inflammatory markers. The latter have also been shown to have effects on the bone and cartilage structures, preventing bone deformities in experimental studies. Table 1 presents in detail these effects.

OBJECTIVE

The primary aim of this study is to demonstrate the inflammation-lowering effect of oral antidiabetic drugs, namely the CRP, ESR and DAS28 levels. The secondary aim was to show that these effects are dependent on the dose of the antidiabetic drug.

METHODS

Subjects

The study has an analytical, observational, case-control design. The information was gathered from the case reports of the patients who were admitted in Sf. Maria Clinical Hospital in Bucharest, beginning with 2010 and until May 2016.

The inclusion criteria for the case group were the presence of RA following the 1987 American College of Rheumatology definition or 2010 ACR-EULAR diagnostic criteria for RA and that of T2DM following WHO diagnosis criteria. Subjects fulfilling only the RA diagnosis criteria were included in the control group. The exclusion criteria were significant hepatic or renal impairment, congestive heart failure (NYHA class III or IV), chronic or acute infections, acute myocardial infarction in the last year or cancer.

TABLE 1. *Antiinflammatory effects of oral antidiabetic drugs*

Drug class	Antiinflammatory effects (22)
Biguanides	1. Lowers vascular adhesion 2. Lowers immune cells proliferation by lowering the levels of oxidised lipids 3. Stimulation of gene expression responsible for cellular antioxidant defences and stimulation of enzymes responsible for nitric oxide formation 4. Inhibits proinflammatory response and the activation of NF-KB pathway 5. Inhibits the differentiation of monocytes in macrophages 6. Lowers the levels of chimerin 7. Lowers CRP level in patients with impaired glucose tolerance 8. Lowers systemic inflammation levels in patients with polycystic ovary syndrome
Sulfonylureas	1. Lowers atherosclerotic plaque inflammation level by inhibiting NF-kB pathway in macrophages 2. Gliclazid lowers endothelial activation and inflammation
Meglitinides	1. Repaglinide lowers PAI-1, hs-CRP, in patients with T2DM 2. Netaglinide has no antiinflammatory effects 3. Mitiglinide lowers IL-6, IL18 şi TNFα
Alpha-glucosidase inhibitors	1. Acarboze does not modify the level of adiponectin, insulin sensitivity or inflammation markers 2. Miglitol lowers the gene expression of cytokines in leucocytes
Tiazolidindione	1. Pioglitazone has antiinflammatory, antithrombotic and anticoagulant effects 2. Reduces the level of inflammatory markers in adipose tissue, liver and atherosclerotic plaque 3. Pioglitazone lowers the overall number of macrophages in the adipose tissue 4. Rosiglitazone, by inhibiting NF-kB pathway, stabilises the atherosclerotic plaque 5. Lowers CRP levels 6. Lowers hs- CRP, carothidian intima-media thickness 7. Rosiglitazone rises the adiponektin levels and lowers IL-6, IL-18 in patients with metabolic syndrome
Gliptins	1. Supresses TLR4, IL-1 by inhibiting PKC 2. Sitagliptin inhibits the progression of atherosclerotic plaque by lowering the expression of TNFα, endotoxic receptors, TLR4, TLR2, JNK1, CRP, IL6, free fatty acids 3. Vildagliptin has antiinflammatory, antithrombotic and anticoagulant effects 4. Vildagliptin lowers IL6, IL8 in patients treated with metformin 5. Linagliptin lowers uric acid levels in patients undergoing hemodialysis
SGLT2 inhibitors	1. Lowers inflammation, oxidative stress and hyperlipidaemia in T2DM rats

Nuclear factor kB (NF kB), C reactive protein (CRP), Plasminogen Activator Inhibitor 1 (PAI1), high sensitivity CRP (hs-CRP), type 2 Diabetes Mellitus (T2DM)Interleukin (IL), Tumor Necrosis Factor alpha (TNFα), Toll-like receptor (TLR), Protein kiase C (PKC), Jun amino-terminal kinases (JNK)

After the selection phase, there were 20 subjects in the case group and 68 in the control group. In order to limit the interference of confounding variables, for every patient in the case group a person from the control group was chosen who had the same sex and a similar age (± 5 years). This resulted in a case group of 20 subjects (12 that use oral antidiabetics, 6 that follow a diet and 2 with insulin monotherapy) and a control group of 20 subjects who were followed approximately 3 years from the diagnosis of RA. The study protocol complied with the Declaration of Helsinki and all participants signed informed consent.

Variables

For the study we gathered baseline demographic variables such as gender, age, occupation, clinical characteristics, medication and comorbidities at baseline and at the end of study. Disease activity score DAS28 and serum biomarkers of inflammation were noted at every admission, together with the dosages of RA and T2DM therapy.

Statistical considerations and analysis

The statistical analysis was done with SPSS version 23. Conventionally, $p<0.05$ was considered as being significant for all hypothesis tests. Numeric variables were described as means ± standard deviation, or as median. For the group comparison we used the Student t test when the data had a normal distribution and non-parametric tests (Mann-Whitney U test) for variables that were not normally distributed. Extreme values were either taken out of the study or replaced with the next smaller value. A repeated measure analysis of variance was carried out, to point out the different evolution patterns between the control and case groups. In order to assess the linear relationship between dosage of oral antidiabetic and the changes in inflammatory markers values, a linear regression was carried out. The variables that did not have a normal distribution were logarithmically transformed in order to comply to the preconditions of regression tests. Moreover, to predict the values of inflammatory markers depending on the dosage, a general linear model was applied.

RESULTS

Patients' Characteristics

The baseline demographic and clinical characteristics, together with the RA treatment are described in Table 2, and it includes data from all subjects, divided by the presence of T2DM. There were no statistically significant group differences regarding gender, age distribution, type of RA (seropositive/seronegative), use of DMARDs, cortisone, NSAIDS or statins. Moreover, regarding DAS28, CRP and ESR levels at diagnosis, they are lower in the case group, but not at a significant level. The only statistically significant differences are observed when comparing the medians of the blood glucose level, this being with 33.15 mg/dl higher in the case group (95% CI 22.3-44), $t(38)=-6.1$, $p<0,005$) and the BMI level, this being with 4.56 kg/m^2 higher in the case group (95% CI= -1.55, -7.57), $t(38)=-3.07$, $p=0.04$).

TABLE 2. *Baseline characteristics of patients*

	Case Group	Control Group
Gender (females), n (%)	11 (55%)	11 (55%)
Age, years	63.1 ±1.49	62.25±1.8
Follow up, month	30.55± 3.58	33.5±3.49
Occupation **Retired, n (%)** **Without occupation, n (%)** **Employee, n (%)**	 16(80%) 1(5%) 3(15%)	 14 (70%) 3(15%) 3(15%)
Geographical area, urban, n (%)	10 (50%)	13 (65%)
BMI, kg/m^2	31.29 ±2.21	26.16±2.94
DAS 28	3.655 ± 0.78	4.75 ±0.74
ESR, mm/h	38.21 ± 34.5	50.03 ± 16.18
CRP, mg/dl	12.0 ± 8.5	20.8 ± 13.3
Blood glucose, mg/dl	129.98 ±12.7	105.22±10.72
Seropositive, n (%)	14 (70%)	15(75%)
DMARD monotherapy	16 (80%)	17 (85%)
DMARD associated therapy	4 (20%)	3 (15%)
Steroid	11 (55%)	16 (80%)
NSAIDs	10 (50%)	6 (30%)
Lipid lowering	18 (90%)	17 (85)
Antiaggregant	7(35%)	9(45%)
Antihypertensive	15 (75%)	11(55%)

Body Mass Index (BMI), Disease Activity Score 28 (DAS 28), Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Disease-modifying antirheumatic drugs (DMARD), Nonsteroidal anti-inflammatory drugs (**NSAIDs**)

Metformin, Sulfonylureas and RA disease activity

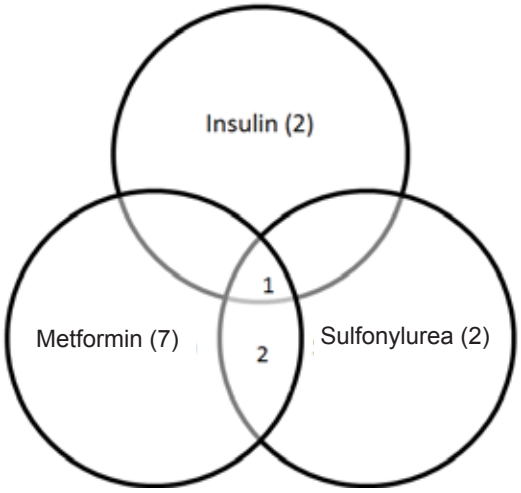
As stated before, the primary objective was to assess the differences between the two groups regarding DAS28, CRP and ESR levels. Taking into consideration the fact that the main oral glucose-lowering drugs were metformin and sulfonylureas, this study focuses only on their effects on the above mentioned dependent variables. Firstly, the population of the study was divided by the presence of oral glucose-lowering agents (OGLA) in the treatment. The

medians of DAS28, CRP and ESR were significantly lower in the group treated with OGLA (2.9 vs 4.06 for DAS28, U=1 391, p<0.005; 11.4 mg/dl vs 2.8 mg/dl for CRP, U=1575, p<0.005; 26.7 mm/h vs 38.5 for ESR, U=1 732.5, p<0.005). Secondly, the presence of metformin both as monotherapy and in combination with other antidiabetic drugs was associated with a statistically significant decrease in the medians of the three dependent variables as follows: 2.8 vs 3.91 for DAS28, 2.8 mg/dl vs. 8.9 mg/dl for CRP, 20 mm/h vs. 33 mm/h for ESR, p<0.005.

The evolution in time of these three variables was noted for the group that used oral glucose lowering agents in parallel with the rest of the population in the study. The first recorded moment was at diagnosis, followed by the moment when an increase (dosage or number of DMARDs) in RA treatment occurred and lastly by the final patients' recording (approximately three years from diagnosis). In the OGLA group, there were significant changes in ESR levels over time (F*(2,6)=585.5, p=0.03), but not in DAS 28 or CRP levels. For the rest of the study group, statistically significant changes over time were seen in DAS28 levels (F(2,10)= 4.792, p=0.03), but not for CRP or ESR levels. Moreover, no significant changes were seen between different time points in either of the study groups. However, a different evolution pattern was noted for the two groups, with a linear and milder evolution for those undergoing treatment with oral antidiabetics (Fig. 2).

F(2,6) – number 2 represents the number of observed moments in rANOVA minus one – (in this case, 3 moments were recorded: at time of admission, the first disease flare's and the last follow-u), and number 6 represents: the multiplication between (number of observed subjects minus one) and (number of observed moments minus one). In this case are practically only 4 patients who had taken oral antidiabetics at all three moments (most did not have available data at the time of admission).*

FIGURE 1. *Venn diagram of antidiabetic treatment distribution in the case group population. Diagram 1 summarizes the baseline oral antidiabetic drug scheme in the case group. There are 6 patients that are following a diet in order to control their diabetes, 2 on insulin therapy, 7 on metformin monotherapy, 2 on sulfonylurea monotherapy, 2 on both metformin and sulfonylurea, 1 in treatment with insulin, metformin and sulfonylurea.*



Comparing the effects of different treatment methods for T2DM in the case group (RA and T2DM), the subjects treated with OGLA had a significantly lower DAS 28 mean than the subjects following a diet for the treatment of T2DM (2.91±0.25 vs. 3.58±0.83, p<0.05). Moreover, metformin as monotherapy resulted in statistically significant differences in the medians of DAS28 and CRP levels, these levels being lower in the monotherapy group (2.7 vs 3.7 for DAS28, U=314, p<0.05 and 2.8 mg/dl vs. 7.5 mg/dl for CRP, U=421, p<0.05). No significant changes in either of these 3 variables were observed when the case group was divided by the presence of sulfonylureas in monotherapy.

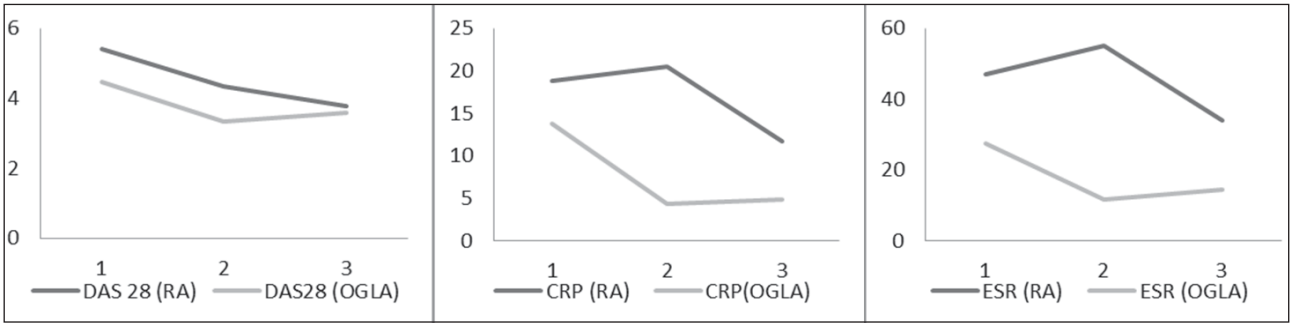


FIGURE 2. *Evolution of the levels of Disease activity score 28 (DAS28), C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the control group (RA) and the case group (OGLA – oral glucose lowering agents). The first moment recorded is at diagnosis, followed by the moment when the RA treatment stepped up and the last one at the end of follow-up.*

These observations underline the beneficial effect of metformin on all the dependent variables, not only in monotherapy, but also in association with other antidiabetic drugs. These changes were not seen in the subgroup treated with sulfonylureas.

Effects are dependent on metformin dosage and BMI

The secondary objective of this study was to asses if the differences in RA activity are dependent on the dosage of oral antidiabetic drugs. With this purpose in view, it was noted that the preconditions of linearity between DAS28, CRP and ESR levels and the metformin dosage/BMI were satisfied. This condition, together with the independence of observations and homoscedasticity were satisfied only by the logarithm of CRP variable. The metformin in mg*m^2/kg can predict the value of CRP (F(1,38)= 8.839, p=0.005), accounting for 18.9% of the variation of CRP (Fig. 3). Moreover, there is a negative correlation between CRP level and metformin in mg*m^2/kg, r=-0.434, p=0.003. Predictions were made in order to determine the value of CRP for the subjects that use 1,000, 2,000 and 2,500 mg metformin daily, for a BMI of 25 kg/m^2. The CRP level for 1,000 mg metformin was 5.72 (95% CI 3.54-9.24) mg/l, for 2,000 mg was 1.43 (95% CI 0.55-3.73) mg/l, and respectively 0.71 (95% CI 0.17-2.87) mg/l for 2,500 mg metformin. Moreover, a negative correlation was also seen between metformin in mg*m^2/kg and CRP value (r(25)=-0.391, p=0.027), when metformin was used in monotherapy.

A linear relationship was also noted between the metformin in mg*m^2/kg and the response to RA therapy, defined as the difference between DAS 28 score from two consecutive determinations. Pearson test of correlation indicated a positive relationship between metformin in mg*m^2/kg and the response to RA therapy, r(10) = 0.547, p=0.051.

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DISCUSSION

The main insights achieved in this study relate to the ability of metformin to significantly lower both DAS28 and CRP level in patients with RA and T2DM, when compared to those that are affected only by RA. Moreover, the subjects from the case group (T2DM and RA) that are under metformin

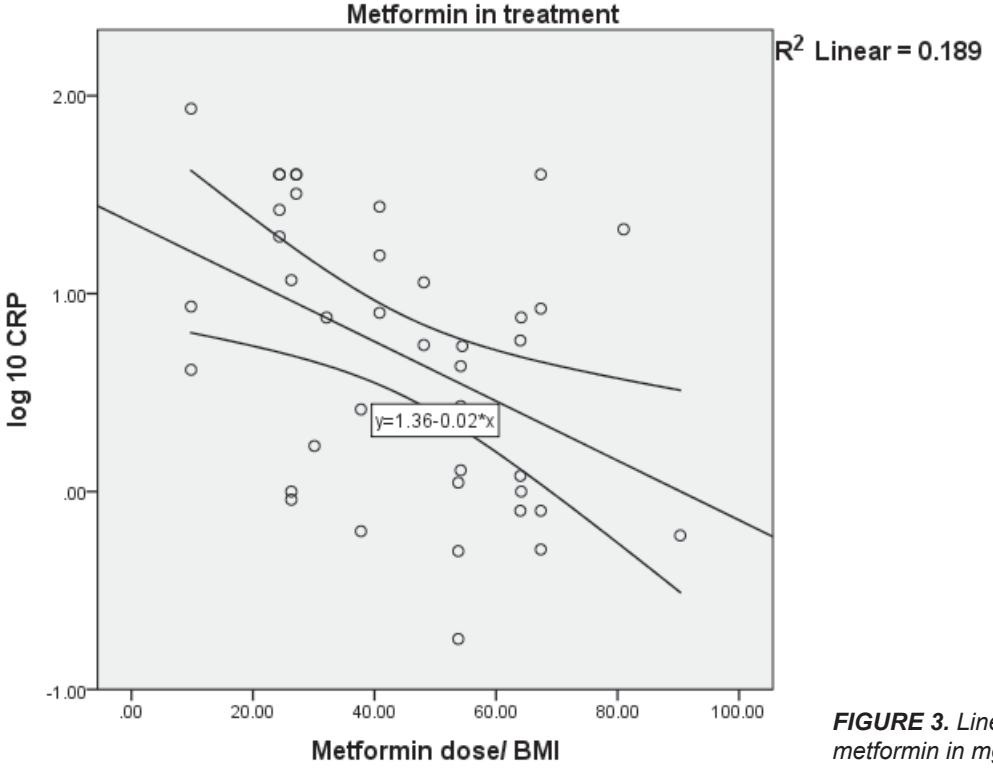

FIGURE 3. *Linear relationship between metformin in mg*m^2/kg and log CRP*

treatment have a lower disease activity score than the subjects that follow a diet. However, in the study were included only 4 patients who were treated with sulfonylureas and therefore no conclusions can be drawn from this group.

In the last several years, oral glucose lowering drugs have gained ever more attention, mainly directed towards their immunomodulatory effects and their ability to lower the cardiovascular morbidity and mortality of T2DM patients. It is a fact that RA patients have an increased CV risk that stems from the increased systemic inflammatory status and the similarity in their pathogenesis. Experimental studies on RA-induced mice have focused on the anti-inflammatory effects of various antidiabetic drugs as metformin (10), gliptins (11,12) and thiazolidinediones (13,14), providing insights on their mechanisms of action regarding this subject.

The clinical effects of these drugs were studied only in a few clinical trials regarding autoimmune diseases. Thiazolidinediones were studied in a randomised, double blind clinical trial on patients with RA without T2DM and they showed a minimum statistically significant decrease in disease activity score, together with a positive effect on the vascular function (15). DPP-4 inhibitors, in a prospective study, have decreased the risk of RA in the group of patients treated with this drug (16). Recently, metformin was used in a randomised trial with patients suffering from Multiple Sclerosis and metabolic syndrome, showing positive results (17).

The main objective of the study was to emphasize the differences in disease activity and inflammatory markers between patients affected by RA (control group) and those affected by both RA and T2DM (case group). By comparing these two groups, the results have shown a decrease in disease activity score and inflammatory markers (CRP and ESR), but not at a significant level. This lack of significance can be explained by the fact that the case group comprised 10% patients who were treated with insulin, 30% subjects that followed a diet, 10% patients that used sulfonylureas as monotherapy and only 50% from subjects that used metformin.

Another test that offered an overview of the evolution of RA patients was the ANOVA test for repeated measures. This test outlined a different pattern of evolution for the patients that were under metformin treatment, with overall lower disease activity markers, a positive initial treatment response and a more stable status of disease activity. As for the subjects in the control group, they have a pronounced increase of disease activity marker values in the evolution of the disease compared to the values at diagnosis. CRP levels at diagnosis were significantly lower than those found during a new disease flare (-3.9 mg/l , p=0.039). The same tendency can be seen for ESR variable (-16.8 mm/h), but without statistical significance.

To highlight the benefits of metformin use in the case group, these patients were compared to the rest of the diabetics who were using other methods for controlling their glucose levels (insulin replacement therapy, diet, or sulfonylureas). The differences between the three studied variables in each group were statistically significant (DAS28 2.8 vs 4, CRP 2.8 mg/l vs. 7.5 mg/l, ESR 20 mm/h vs. 27 mm/h). Approximately the same results can be observed in the case of metformin monotherapy, the median of the DAS 28 and CRP values were significantly lower than the control group (p(DAS)=0.001 and p(CRP)= 0.008. In the case of sulfonylurea, either in monotherapy or when combined, the values of the variables monitored did not show important changes. These findings are in correlation with the international literature, where sulfonylurea drugs showed no anti-inflammatory effects neither in experimental studies nor in clinical ones.

Another hypothesis that this study dealt with was that these differences are dependent on the metformin dose. A negative correlation was found between metformin in $mg*m^2/kg$ and CRP levels, both in monotherapy and associated with other antidiabetic drugs (r=-0.391, p=0.027 and r=-0.434, p=0.003 respectively). Similar results were reported in not only by an experimental study that emphasizes the need to increase metformin dosage in order for it to produce antiinflammatory effects (18), but also in a clinical study that observed metformins' capacity of lowering inflammation markers like CRP, TNFα, IL2 and INFγ (19).

Both groups present a similar distribution of CV diseases and metabolic dysfunctions. The drugs used to treat the mentioned diseases are known for their CRP-lowering effect. This effect was evaluated in this study population, without any significant result. Therefore, we can credit metformin with the CRP-lowering effect, both in monotherapy and in association.

Knowing the arguments brought by randomised clinical trials for the benefits of metformin for the patients with impaired glucose tolerance, T2DM or

metabolic syndrome and taking also into account the high frequency of these comorbidities (20,21), we can accept the need of metformin introduction in the treatment of the patients with T2DM and RA. These benefits can also extend to RA patients without T2DM, but with impaired glucose tolerance or important cardiovascular risk factors. Another element that needs further study is the use of high doses of metformin and their effect on the inflammation markers.

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