

THIAZOLIDINEDIONES IMPROVE INSULIN SENSITIVITY, ADIPONECTINEMIA AND PROINFLAMMATORY STATUS IN TYPE 2 DIABETES MELLITUS

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REZUMAT

În etiopatogeneza diabetului zaharat tip 2 intervin, în proporții variabile de la un caz la altul, deficitul relativ de insulină și insulinorezistența. Aproximativ 92% din pacienții cu diabet zaharat tip 2 prezintă insulinorezistență, perturbare ce se asociază frecvent cu o serie de anomalii biochimice care cresc riscul pentru boli cardiovasculare aterosclerotice: dislipidemie aterogenică, creșterea sintezei citokinelor proinflamatorii, scăderea adiponectiniei, status protrombotic hipofibrinolic, modificări hemodinamice și disfuncție endotelială. Tiazolidindionele sunt o clasă de antidiabetice orale cu proprietăți unice, care cresc sensibilitatea la insulină a țesuturilor periferice, și anume la nivelul țesutului adipos, mușchiiului scheletic, țesutului hepatic și peretelui vascular. Scopul acestui studiu a fost să evalueze efectele tratamentului cu tiazolidindione asupra controlului glicemic, insulinorezistenței și concentrațiilor plasmatice ale adipocitokinelor la pacienții cu diabet zaharat tip 2. La subiecții studiați asocierea unei tiazolidindione la tratamentul pe care îl urmau anterior a determinat următoarele modificări semnificative: reducerea insulinorezistenței, ameliorarea controlului glicemic și a profilului lipidic, scăderea concentrației plasmatice a markerilor inflamației și creșterea adiponectiniei. În plus, s-a evidențiat o corelație inversă între concentrația plasmatică a adiponectinei și cea a unor markeri ai inflamației, fapt ce susține ipoteza că reducerea producerii adiponectinei contribuie la inflamația cronică întâlnită în diabetul zaharat tip 2. Rezultatele obținute sugerează că tiazolidindionele au efecte benefice la pacienții cu diabet zaharat tip 2, întrucât reduc insulinorezistența, ameliorează controlul glicemic și influențează pozitiv majoritatea factorilor de risc cardiovascular asociați sindromului de insulinorezistență.

Cuvinte cheie: diabet zaharat tip 2, obezitate, insulinorezistență, adiponectină, inflamație, tiazolidindione

ABSTRACT

Two core metabolic defects contribute to the development of type 2 diabetes mellitus: relative insulin insufficiency and insulin resistance. Approximately 92% of patients with type 2 diabetes demonstrate insulin resistance which is associated with a cluster of abnormalities that increase the risk for atherosclerotic cardiovascular disease: dyslipidemia, increased expression of proinflammatory cytokines, decreased plasma levels of adiponectin, activation of procoagulants, hemodynamic changes and endothelial dysfunction. The thiazolidinediones are a unique class of oral antidiabetic agents that has been shown to directly reduce insulin resistance at sites of insulin action, specifically adipose tissue, skeletal muscle, liver and vascular wall. The purpose of our study was to evaluate the effect of treatment with thiazolidinediones on glycemic control, insulin resistance and plasma levels of adipocytokines in patients with type 2 diabetes mellitus. In study subjects, adding a thiazolidinedione to their previous treatment produced the following significant changes: improved insulin sensitivity, glycemic control and lipid profile, decreased plasma levels of inflammatory markers and increased plasma adiponectin. We found a negative correlation between adiponectinemia and plasma levels of inflammatory markers, finding that may suggest that decreased production of adiponectin contributes to the systemic and vascular inflammation commonly found in type 2 diabetes mellitus. The results of our study indicate that treatment with thiazolidinediones is beneficial in type 2 diabetes mellitus, as these drugs reduce insulin resistance, improve glycemic control and positively influence many of the cardiovascular risk factors associated with the insulin resistance syndrome.

Key Words: type 2 diabetes mellitus, obesity, insulin resistance, adiponectin, adipocytokines, proinflammatory status, thiazolidinediones

INTRODUCTION

The adipose tissue is far from being just a simple storage facility for triglycerides and constitutes a true endocrine organ as it produces a number of hormones

and other biologically active peptides (some of them exclusive for the adipocytes) that play an essential role in regulating fuel as well as fat and carbohydrate metabolism. These substances are generically called "adipokines": leptin, tumor necrosis factor alfa (TNF α), plasminogen activator inhibitor 1 (PAI-1), interleukin 6 (IL-6), adipisin, resistin, adiponectin etc.^{1,2}

Visceral obesity is associated with severe metabolic alterations, such as dyslipidemia, insulin resistance and type 2 diabetes mellitus (DM) and with an increased cardiovascular risk. In the pathogenesis of these conditions a major role could be attributed to a deregulated adipocytokine synthesis following the changes in fat tissue mass. In obese states, most

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of the adipocytokines are present in increased concentrations: resistin, PAI-1, TNF α and IL-6, and have a proinflammatory effect contributing to the development of the complications of obesity, such as insulin resistance and atherogenesis.^{2,3}

A special place among adipocytokines is reserved to adiponectin, a collagen-like protein produced exclusively in the adipocytes, that plays an important role in modulating tissue sensitivity to insulin and also exerts protective, antiinflammatory and antiatherogenic actions.^{2,4,5}

The insulin resistance syndrome is a heterogeneous disorder characterized by the presence of hyperinsulinemia, impaired glucose tolerance or type 2 DM, essential hypertension, dyslipidemia, visceral adiposity, and/or hypercoagulability. This clustering of cardiovascular risk factors leads to a high rate of coronary events and increased mortality in this population.

The thiazolidinediones are a unique class of oral antidiabetic agents that has been shown to directly reduce insulin resistance at sites of insulin action, specifically adipose tissue, skeletal muscle, liver and vascular wall. By reducing insulin resistance, these drugs influence many of the modifiable cardiovascular risk factors associated with the insulin resistance syndrome, also known as the metabolic syndrome.^{6,7}

MATERIALS AND METHODS

The purpose of our study was to evaluate the effect of treatment with thiazolidinediones on insulin resistance, glycemic control and plasma levels of adipocytokines in patients with type 2 DM.

The study enrolled 36 patients with type 2 DM and metabolic syndrome (17 women and 19 men) treated with oral antidiabetic drugs (other than PPAR γ agonists) and poor glycemic control.

Subjects eligible for participation in this clinical trial were:

- Men or women ≥ 35 years of age with a diagnosis of type 2 diabetes (based on World Health Organization criteria);
- Fasting triglyceride levels ≥ 150 mg/dL and < 600 mg/dL;
- Fasting LDL cholesterol levels < 160 mg/dL;
- HbA_{1c} values ≥ 7 and $\leq 11\%$.

Subjects were excluded from participation in this study for any of the following:

- Treatment within 60 days of screening with insulin, systemic glucocorticoid therapy, combination oral antihyperglycemic therapy, or any weight loss agent;

- Known allergy to any thiazolidinedione;
- Serum creatinine ≥ 176.8 $\mu\text{mol/dL}$ (≥ 2.0 mg/dL);
- Alanine aminotransferase or aspartate aminotransferase ≥ 1.5 times the upper limit of normal or significant clinical liver disease;
- Hemoglobin < 10.5 g/dL (females) or < 11.5 g/dL (males) at screening;
- Functional New York Heart Association Cardiac Disease Class III or IV, history of CVD, or heart surgery within 6 months of screening;
- Receiving renal dialysis;
- Current therapy for malignancy other than basal cell or squamous cell skin cancer;
- Signs or symptoms of drug or alcohol abuse;
- Any condition or situation precluding adherence to and completion of the protocol;
- For female subjects: pregnancy, breast-feeding, or the intent to become pregnant during the study period prohibited participation.

In study subjects, rosiglitazone 4-8 mg daily was associated to the previous treatment. All treatment regimens of concurrent medications received with potential effects on lipid profile (e.g. statins, fibric acid derivatives, antihypertensives, diuretics, hormone therapy, weight-loss products, etc) either remained unchanged or were not initiated during the study.

Before starting the treatment with rosiglitazone and after 16 weeks of therapy the following analyses were performed:

- Triglycerides, total cholesterol, and plasma glucose in blood samples (following at least 10 h of fasting) using standard enzymatic methods;
- HDL and LDL cholesterol by direct methods;
- HbA_{1c} by chromatography;
- Total insulin by enzyme-linked immunosorbent assay (ELISA);
- Highly sensitive C-reactive protein (hs-CRP) by immunonephelometry ;
- IL-6, TNF- α were assessed by ELISA;
- Adiponectin plasma levels were measured by radioimmunoassay;
- Surrogates of insulin resistance and β -cell function were estimated by homeostasis model assessments.

The following clinical measurements were made at baseline and at follow-up:

- Blood pressure was assessed as the average of 2 measurements taken after subjects had been seated for 5 minutes;
- Waist circumference was measured in subjects in a standing position at the level of the umbilicus;
- Body weight and height.

RESULTS

In patients with type 2 DM thiazolidinediones decreased HbA_{1c} ($p < 0.001$) and fasting plasma glucose ($p < 0.01$) and improved insulin sensitivity ($p < 0.001$). (Fig. 1)

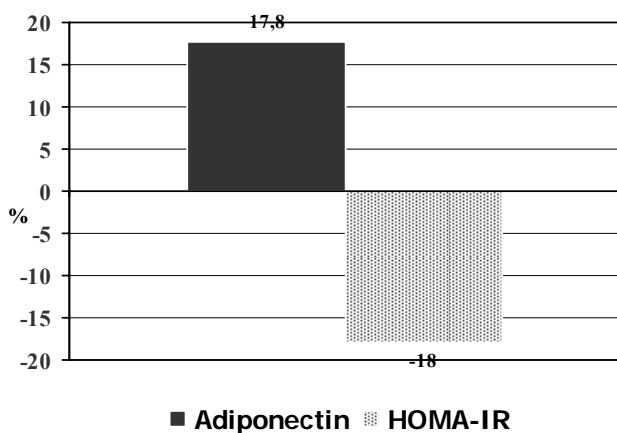


Figure 1. Changes of adiponectinemia and insulin resistance after 16 weeks of treatment with rosiglitazone.

Fasting plasma triglycerides were reduced from the baseline value of 246 ± 25.32 mg/dL to 201 ± 19.42 mg/dL ($p < 0.01$). In addition, plasma levels of inflammatory markers decreased significantly, as it follows: TNF- α with 16.2%, IL-6 with 18.3%, hs-CRP with 19.4%, while plasma adiponectin increased with 17.8%. (Fig. 1) Plasma levels of total cholesterol and LDLc increased, but not significantly. (Table 1)

Table 1. Characteristics of study subjects at baseline and after 16 weeks of treatment with rosiglitazone.

Parameter	Baseline	Follow-up	p
Body weight (kg)	82.3 ± 12.4	84.1 ± 11.2	> 0.05
F	88.6 ± 16.3	91.3 ± 17.4	> 0.05
M			
Fasting plasma glucose (mg/dL)	224.3 ± 8.3	172.5 ± 7.4	< 0.001
HbA _{1c} (%)	8.7 ± 1.2	7.9 ± 1.1	0.001
Total cholesterol (mg/dL)	195.4 ± 23.9	203.5 ± 25.4	0.082
Triglycerides (mg/dL)	246.5 ± 25.3	201.4 ± 19.4	< 0.001
HDLc (mg/dL)	39.3 ± 5.3	44.8 ± 6.2	< 0.001
LDLc (mg/dL)	108.4 ± 15.2	115.6 ± 12.3	0.05
Systolic blood pressure (mm Hg)	138.4 ± 32.2	130.2 ± 31.9	< 0.05
Diastolic blood pressure (mmHg)	87.4 ± 14.1	80.3 ± 17.4	< 0.05
hs-CRP	7.9 ± 2.3	4.8 ± 1.9	< 0.001
Fibrinogen	345.4 ± 63.3	293.5 ± 59.5	< 0.001
IL-6	7.2 ± 1.6	4.8 ± 0.9	< 0.001
TNF- α	9.3 ± 2.1	7.2 ± 1.3	< 0.001

Data are means \pm SD or n (%). P was calculated with unpaired Student's t tes

We have found a negative correlation between adiponectinemia and plasma levels of IL-6. (Fig. 2)

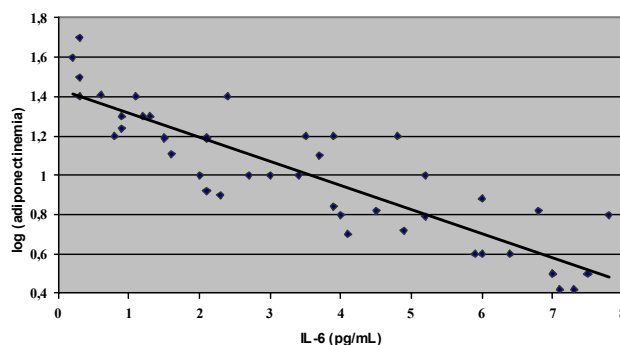


Figure 2. Correlation between adiponectinemia and plasma levels of IL-6.

DISCUSSION

Our results indicate that rosiglitazone significantly improves insulin sensitivity and glycemic control in patients with type 2 DM. Thiazolidinediones have proven to be effective oral medications in the treatment of insulin resistance and type 2 DM.⁸ They improve insulin sensitivity by interacting with a family of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs), particularly PPAR γ .⁶ Thiazolidinediones are thought to enhance the actions of insulin by increasing insulin-dependent glucose disposal in muscle and fat, to a lesser extent, which reduces hepatic glucose production.⁶

Rosiglitazone also produced improvements in several cardiovascular risk factors, including triglycerides, HDL cholesterol, fibrinogen and hs-CRP. In addition, we found a substantial and statistically significant reduction in blood pressure after rosiglitazone treatment.

Increased insulin resistance is associated with increased plasma levels of inflammatory markers such as IL-6, hs-CRP and TNF- α .⁹ Especially IL-6 and hs-CRP are established risk markers for cardiovascular events. As several cytokines are also produced by adipose tissue, it was postulated that an "adipovascular" axis may contribute to the increased risk of cardiovascular events in type 2 diabetic patients.¹⁰ Recent studies suggest that adiponectin may play a role in the modulation of inflammatory vascular response by inhibiting the expression of adhesion molecules on endothelial cells, inhibiting endothelial cell NF- κ B signaling, and suppressing macrophage function.^{4,11}

Given the anti-inflammatory and vasculoprotective actions of adiponectin and the presentation of type 2 DM as a chronic inflammatory state, the inverse association between decreased plasma adiponectin levels and increased plasma levels of hs-CRP and of IL-6 in our study is not surprising.^{4,10,12} Thus, our finding of an independent inverse correlation between plasma levels of adiponectin and IL-6 and, respectively,

hs-CRP may suggest that decreased production of adiponectin contributes to the systemic and vascular inflammation commonly found in type 2 DM.

CONCLUSIONS

Treatment with PPAR γ agonists is beneficial in type 2 DM, as these drugs reduce insulin resistance, improve glycemic control and lipid metabolism, decrease proinflammatory status and ameliorate endothelial function.

As knowledge of pleiotropic effects of these agents advances further potential indications are being revealed, including role in the management of cardiovascular disease and metabolic syndrome.

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