Beneficial effects of combined treatment with rosiglitazone and exercise on cardiovascular risk factors in patients with type 2 diabetes

Nikolaos PE Kadoglou, MD, Fotios Iliadis, MD, Christos D Liapis MD, FACS, FRCS, Despina Perrea, PhD, Nikoleta Angelopoulou, MD, Miltiadis Alevizos, MD.

1st Propedeutic Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece
Vascular Surgery, University Medical School, Athens, Greece
Laboratory of Experimental Surgery and Surgical Research, University of Athens, Greece
Physical Education and Sports Science, Aristotle University of Thessaloniki, Greece

Correspondence:
Nikolaos PE Kadoglou
124 Vosporou str, 54454 Thessaloniki Greece.
Email: nikoskad@yahoo.com

ClinicalTrials.gov Identifier: NCT00306176

Received for publication 2 February 2007 and accepted in revised form 12 June 2007.
Physical activity attenuates metabolic and cardiovascular maladaptations in diabetes mellitus (DM), by improving glycemic control, insulin resistance, cardiorespiratory fitness and adipocytokines levels (adiponectin, resistin, tumour necrosis factor-a/TNF-a, interleukin-6/IL-6) (1,2). Likewise, thiazolidinediones (TZDs) influence favourably the above indexes (3,4). We hypothesized that the combination of exercise training and rosiglitazone, a member of TZDs, would confer additional benefits in metabolic and cardiovascular profile of diabetic patients, exceeding those of each treatment alone.

Research Design and Methods

Subjects

One-hundred Caucasians overweight/obese patients (BMI> 25kg/m²) with type 2 DM consented to participate. They were treated with half-maximal doses of metformin(1700mg) and gliclazide(180mg), for at least 6 months, with eventually poor glycemic control (HbA1c>7%). Smokers and patients receiving lipid lowering medications, insulin or thiazolidinediones were rejected. Those with vascular complications, life-threatening diseases, orthopedic problems, heart, liver and renal impairment were also excluded. After baseline examination, participants were randomized to the following age and sex-matched groups: 1) CO(N=25): Control group. 2) EX(N=25): 8-months exercise training. 3). RSG(N=25): Adjunctive therapy with rosiglitazone (8mg/day). 4) RSG+EX(N=25): 8-months exercise program (as in EX) and simultaneous treatment with rosiglitazone (8mg/day).

The prescription of exercise program was based on baseline ergocycle testing results and its workload was gradually increased, until patients achieved 50-80% VO2peak, 45-60min, 4 sessions/week (5). After the 4th week the intensity and duration of each session remained constant. Patients of the 1st and 3rd group were instructed to maintain their habitual activities.

Laboratory and clinical measurements

Blood samples were obtained at baseline and at the end of the study. All participants avoided any severe physical activity 48 hours before measurements. Plasma adiponectin (R&D Systems Inc., USA), resistin (BioVendor Laboratory Medicine Czech Republic), insulin (DRG Diagnostics, Germany), IL-6 and TNFa (Assay Designs Inc., USA) concentrations were assayed using ELISA kits. The intra- and inter-assay CVs are provided by manufacturers. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR)(6). Samples were frozen and stored (-80°C) until analysis in the same assay. Cardiorespiratory capacity was assessed at baseline and at the end of the study with a graded symptom-limited exercise test on electronically-braked ergocycle, using gas exchange analyzer (COSMED K4, Italy)(7).

Statistical analysis

Comparison between groups of baseline, final values and changes of variables was performed by one-way ANOVA and post-hoc Tukey test (2x2 factorial design). Changes within groups were analyzed by Wilcoxon signed-rank test. Normality of distribution was assessed by Kolmogorov-Smirnov test. P value of <0.05 was considered statistically significant.

Results

Interventions effects
Baseline values of all variables and the concomitant medications did not differ between groups. Five patients discontinued the study due to personal reasons. Finally ninety-five patients were eligible for analysis. No adverse events were referred.

Compared to baseline and EX group rosiglitazone treatment increased BMI significantly (p<0.001). No substantial changes were noted in the other groups. Exercise training increased exercise capacity (VO2peak) by 14.9%(p<0.001), while rosiglitazone induced a modest (5.46%), but significant improvement of fitness compared to either baseline (p<0.001) or control group (p=0.031). Importantly, combined therapy, increased VO2peak remarkably (26.48%;p<0.001), which exceeded the complementary effects of both interventions.

Although both rosiglitazone treatment and exercise training alone ameliorated glycemic indexes, fasting insulin and HOMA-IR (p<0.05), RSG+EX group elicited more pronounced decrease of the aforementioned parameters compared to all groups (p<0.05)(table 1).

**Adipocytokines**

We observed considerable reduction of resistin and IL-6 levels in all interventions groups (p<0.05), but greater alterations were found in RSG+EX group. Moreover combined therapy and rosiglitazone elicited significant increment of adiponectin in comparison to baseline and other groups (p<0.05). Similarly TNF-a was also downregulated significantly in the latter groups and compared to CO group the change was significant only after combined treatment. Patients in EX group demonstrated a slight increase of adiponectin (p=0.39) and a less marked decrease of TNF-a (p=0.45). All adipocytokines were not affected significantly in CO group.

**Conclusions**

In this 8-month study we demonstrated for first time that simultaneous treatment with rosiglitazone plus exercise attenuated adipocytokines levels, counteracted rosiglitazone-induced weight gain and extended improvements of insulin sensitivity, glycemic control and fitness beyond those expected by their complementary actions in patients with type 2 DM.

The most pronounced results of glucose regulation were observed in RSG+EX group (HbA1c:-19.1%). After completion of the study 78% of patients in RSG+EX, 37.9% in RSG and 21.82% in EX group had achieved glycemic target (HbA1c<7%). This is a striking finding regarding that our patients had inadequate glycemic control notwithstanding the double antidiabetic treatment. Furthermore combined treatment ameliorated considerably insulin resistance (δHOMA-IR:-68.1%) exceeding the expected results from the addition of rosiglitazone (δHOMA-IR:-30.8%) to exercise (δHOMA-IR:-23.08%). We hypothesized that the latter synergistic effects might be ascribed to multiple interactions on insulin signalling and muscle glucose uptake (8,9).

Poor metabolic control, physical inactivity and muscle abnormalities are determinants of impaired exercise capacity in type 2 DM (1,10). To our knowledge this is the first study demonstrating a robust increase of fitness in RSG+EX group, outlining synergism between TZDs and exercise training. Trying to explain these results we observed that VO2peak increment was correlated with HOMA-IR and HbA1c reduction in all active groups (data not shown). We then postulated that metabolic control improvement after combined treatment might amplify VO2peak elevation. Alternatively TZDs and physical activity have been demonstrated to ameliorate endothelial
dysfunction and induce mitochondrial biogenesis and thereby could facilitate oxygen delivery and muscle performance (1,11,12).

Adiponectin modulates insulin sensitivity with significant anti-atherogenic properties (13). Our lifestyle intervention left almost unaltered adiponectin, while rosiglitazone treatment doubled adiponectin levels (14). Therefore the increment of adiponectin in RSG+EX was predominantly ascribed to rosiglitazone administration.

Up to now limited studies provide conflicting data about the influence of TZDs and prolonged exercise on human plasma adipocytokines (5,15-19). We demonstrated that all interventions suppressed resistin and IL-6 levels, while combined therapy and rosiglitazone alone decreased TNF-α levels significantly. Those effects were independent of insulin resistance modulation. Among all groups the greatest magnitude of anti-inflammatory impact was found in RSG+EX, which raises the prospect of reduced cardiovascular risk.

Weight gain, the most common side effect of TZDs, is predominantly attributed to fluid retention (3). In RSG+EX group body-weight remained stable. Perhaps the addition of exercise counterbalanced the rosiglitazone-related body-weight increase by decreasing remarkably fat-mass content.

The principal limitation of our study was the small number of patients. However the sample cohort was adequately homogeneous. Another limitation was the usage of HOMA-IR index. Although it is dependent on both peripheral and hepatic insulin sensitivity, it highly correlates with estimation derived from euglycemic clamp test (6). The combination of rosiglitazone and exercise favoured remarkable benefits on traditional and novel cardiovascular risk factors. Further research will confirm the aforementioned promising results.

Acknowledgments

This study was financially supported by the project “Pythagoras I” (Greek Ministry of National Education and Religious Affairs and European Union). Nikolaos PE Kadoglou was granted by Propondis Foundation.
REFERENCES

<table>
<thead>
<tr>
<th>Group</th>
<th>CONTROLS</th>
<th>EX</th>
<th>RSG</th>
<th>RSG+EX</th>
<th>P1</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 0</td>
<td>Week 0</td>
<td>Week 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(M/F)</td>
<td>23 (9/14)</td>
<td>23 (8/15)</td>
<td>25 (10/15)</td>
<td>24 (9/15)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.32±9.28</td>
<td>56.91±7.09</td>
<td>59.04±7.35</td>
<td>57.83±7.61</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>D.D. (years)</td>
<td>5.78±2.91</td>
<td>6.83±3.69</td>
<td>5.29±2.63</td>
<td>6.33±2.25</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>193.16±25.92</td>
<td>190.32±33.59</td>
<td>198.59±43.91</td>
<td>189.64±28.09</td>
<td>**&lt;0.001</td>
<td>c&lt;0.001, c&lt;0.001, c&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.03±0.91</td>
<td>8.02±1.16</td>
<td>8.53±1.26</td>
<td>8.29±1.07</td>
<td>**&lt;0.001</td>
<td>a0.019, b0.005, f0.028</td>
</tr>
<tr>
<td>Fasting Insulin (mU/L)</td>
<td>12.98±4.68</td>
<td>12.03±3.67</td>
<td>12.97±4.85</td>
<td>12.78±4.52</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.19±2.72</td>
<td>5.65±2.14</td>
<td>6.63±2.65</td>
<td>6.17±2.71</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>23.62±6.32</td>
<td>22.43±4.4</td>
<td>23.68±4.0</td>
<td>22.56±3.13</td>
<td>**&lt;0.001</td>
<td>a0.048, b0.045, c0.009</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>9.27±1.77</td>
<td>8.94±1.50</td>
<td>9.55±1.05</td>
<td>8.15±1.52</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>7.90±2.33</td>
<td>8.53±3.48</td>
<td>6.86±2.63</td>
<td>7.15±3.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>18.16±5.61</td>
<td>17.07±6.21</td>
<td>17.48±8.12</td>
<td>18.53±6.8</td>
<td>**&lt;0.001</td>
<td>a0.043, b0.045, c0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5.0±3.42</td>
<td>4.8±3.75</td>
<td>4.7±3.46</td>
<td>4.4±3.14</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TNFa (pg/ml)</td>
<td>92.81±47.05</td>
<td>91.91±42.18</td>
<td>88.61±41.88</td>
<td>94.10±49.98</td>
<td>0.048</td>
<td>c0.01, d0.011</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.96±1.03</td>
<td>31.14±3.58</td>
<td>30.04±2.99</td>
<td>29.91±1.78</td>
<td>0.006</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass %</td>
<td>38.8±9.4</td>
<td>37.9±7.5</td>
<td>38.6±8.7</td>
<td>39.5±8.2</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SEM. M/F: male/female; D.D., duration of diabetes; FPG, Fasting plasma glucose; HOMA-IR, homeostasis model assessment for insulin resistance; P1, p values of levels of variables between baseline vs the end of the study within groups; *P<0.05, **P<0.001, NS, Not Significant; P1, ANOVA of changes of variables between groups; a, b, c, d, e, f, Post-hoc analysis of changes of variables between groups; a RSG+EX vs RSG, b RSG+EX vs EX, c RSG+EX vs C, d RSG vs EX, e RSG vs C, f EX vs C.