Comparison of metformin, gliclazide MR and rosiglitazone in monotherapy and in combination for type 2 diabetes

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ABSTRACT

Objective: To compare the efficacy and tolerability of metformin, rosiglitazone and gliclazide MR as monotherapy and in combination in the treatment of type 2 diabetes. Subjects and methods: 250 patients treated with oral antidiabetic agents for at least 24 weeks in monotherapy or in combination therapy were included in this retrospective study. Results: As monotherapy the reduction of fasting plasma glucose (FPG), postprandial glycemia (PPG) and HbA1c was similar with the three drugs after 24 weeks. Among patients on combination therapy, the reduction in HbA1c, FPG and PPG was significantly lower with rosiglitazone plus metformin, as compared to metformin plus gliclazide MR or gliclazide MR plus rosiglitazone. Patients treated with rosiglitazone achieved less favorable changes in lipid profile. Conclusion: In monotherapy all drugs were equally effective in improving glycemic control, whereas the combination of metformin plus gliclazide MR provided the best results concerning the improvement of both, glycemic control and lipid profile.

Keywords

Metformin; gliclazide MR; rosiglitazone

INTRODUCTION

The main pathophysiologic mechanisms of hyperglycemia in type 2 diabetic patients involve insulin resistance, impaired insulin secretion and increased hepatic glucose output (1-3). The three main options among oral glucose-lowering drugs are metformin, sulphonylureas and thiazolidinediones (TZDs). They may be used as single-agent therapy, but the majority of patients will eventually require combination therapy to achieve an appropriate glycemic control (4-7).
has been some discussion on the best initial drug therapy for type 2 diabetes, but most authors choose metformin due to its efficacy, safety and lower cost (8-10).

Although metformin counteracts peripheral insulin resistance its major antihyperglycemic effect is to decrease hepatic glucose output (11,12). Typically, metformin monotherapy will lower glycated hemoglobin (HbA1c) by ~1.5 percentage points (11,12). It is generally well tolerated with the most common adverse effects being gastrointestinal disturbances. The most feared complication is lactic acidosis, though extremely rare (less than 1 case per 100,000 treated patients) (9,11). The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast to most blood glucose-lowering medications (5,6). The UKPDS demonstrated that metformin therapy significantly reduced the risk for microvascular and macrovascular diabetic complications (13,14).

Sulphonylureas are widely used to treat type 2 diabetes because they stimulate insulin secretion by pancreatic beta-cells (5,15). Hypoglycemia and weight gain are the main related inconveniences (4). Gliclazide is a second generation sulphonylurea while gliclazide-modified release (gliclazide MR) is a new formulation of this drug designed for once-daily administration (16,17). As monotherapy, gliclazide MR provides a 0.9%-1.8% reduction in HbA1c (16). Intensive treatment of diabetes with gliclazide MR in the study ADVANCE resulted in significant reduction of microvascular complications (18). Gliclazide MR causes less hypoglycemia than chlorpropamide and glibenclamide (16,19). In the GUIDE study (20), the rate of hypoglycemia was significantly lower with gliclazide MR as compared to glimepiride.

Rosiglitazone and pioglitazone are members of the TZD drug class. They are synthetic ligands that bind to the nuclear peroxisome proliferator-activated receptor-gamma (PPARγ) and reduce insulin resistance and glucose levels by increasing the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin (21-24). When used as monotherapy TZDs reduced HbA1c levels by 0.5-1.4 percentage points (7,23). The most common adverse effects of TZDs are fluid retention and weight gain (24).

For patients who do not take insulin, accumulating evidence suggests that the combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective in achieving and maintaining target plasma glucose and HbA1c levels (25,26). However, there has been some debate on which combination therapy would be more effective (26,27).

The main objective of the present study was to evaluate the efficacy and tolerability of metformin, gliclazide MR and rosiglitazone as monotherapy and in combination in the management of type 2 diabetes.

SUBJECTS AND METHODS

Study cohort

A retrospective analysis of medical records was performed on patients with type 2 diabetes undergoing routine follow-up surveillance in the Division of Endocrinology of Hospital das Clinicas, Universidade Federal de Pernambuco, and in Pernambuco Diabetes and Endocrinology Center, located in Recife, Brazil, from 2000 to 2008. All patients treated with oral antidiabetic drugs for at least 24 weeks in monotherapy or in combination therapy without the concomitant use of lipid-lowering drugs were included in this study.

Study design and assays

The main objective of this study was to compare the efficacy of different treatments with oral glucose-lowering drugs regarding the improvement of glycemic control and lipid profile after 24 weeks. We also aimed at evaluating their effect on body weight and on the frequency of symptomatic hypoglycemia, gastrointestinal (GI) side effects, ankle edema, as well as cardiac complications.

Monotherapy with metformin, gliclazide MR or rosiglitazone was started in patients who did not respond to lifestyle intervention. Combination therapy was prescribed to patients whose monotherapy was not able to maintain HbA1c levels < 7%. It consisted of dual therapy with metformin plus gliclazide MR, gliclazide MR and rosiglitazone, or metformin plus rosiglitazone.

Body mass index (BMI), HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and lipid profile were evaluated at baseline and every three months afterwards. All plasmatic parameters were determined after a 12-hour overnight fast, except that of PPG that were obtained two hours after lunch. Venous blood samples were taken from all patients between 8 a.m. and 9 a.m. Total cholesterol (TC), HDL-cholesterol, triglycerides (Tg), and plasma glucose were measured by immunoturbidimetric methods using commercial kits (Selectra Merck), with intra- and inter-assay coefficients of variation (CV) < 2%. The LDL-cholesterol (LDL-C) concentration was calculated by the Friedewald formula (28). HbA1c levels were
measured by a high-performance liquid chromatography method (DIAMAT, Bio-Rad, USA; normal values, 4.0%-6.0%), with intra- and inter-assay CV < 2%. BMI was calculated as weight in kilograms divided by the square of height in meters.

Patients in use of lipid-lowering drugs were excluded from the study in order to allow a better interpretation of the effect of oral antidiabetic drugs on the lipid profile.

The study was performed according to the declaration of Helsinki and was approved by the local ethics committee. All study participants gave their informed consent for inclusion in the study.

Statistical analysis

In the analysis of qualitative variables, χ² test or Fisher’s exact test were used whenever necessary. Student’s t-test or the analysis of variance (ANOVA) was performed for the comparative analysis of quantitative variables. Results are presented as mean values ± SD. The value of p < 0.05 was considered statistically significant.

RESULTS

Demographic, clinical and laboratorial features of the patients

A total of 250 patients was enrolled in this study, of whom 130 (52%) were females and 120 (48%) males (p = 0.689). Their age ranged from 38 to 65 years (mean, 50.2 ± 19.2). According to the type of treatment, patients were subdivided into six groups: 60 (24%) were treated with metformin (850-1000 mg twice daily), 40 (16%) with gliclazide MR (60-90 mg/day), 25 (10%) with rosiglitazone (4 mg twice daily), 65 (26%) with gliclazide MR (60-90 mg/day) plus metformin (850-1000 mg twice daily), 30 (12%) with metformin (850-1.000 mg twice daily) and rosiglitazone (4 mg twice daily), and 30 (12%) with gliclazide MR (60-90 mg/day) plus rosiglitazone (4 mg twice daily).

As shown in table 1, BMI, baseline glycemic control and lipid profile did not differ significantly in patients submitted to monotherapy. The same was true for those that received combination therapy (Table 2).

Effect of monotherapy on glycemic control, lipid profile and body weight

The reduction of FPG, PPG and HbA1c was similar with the three drugs after 24 weeks (Table 3). However, at Week 12, the decrease of HbA1c levels was less pronounced with rosiglitazone (Figure 1). Conversely, the improvement in lipid profile was of lesser magnitude in the rosiglitazone group and similar in patients treated with metformin or gliclazide MR. Moreover, weight change greatly differed as there was a weight loss of 4.2 ± 0.9 kg in the metformin group but a weight gain in the other groups (p < 0.001).

Effect of combination therapy on glycemic control, lipid profile and body weight

As shown in table 4, the reduction of FPG, PPG and HbA1c, as well as the improvement in lipid profile, were less evident in patients treated with metformin plus rosiglitazone, whereas the improvement in lipid profile was stronger in the metformin-gliclazide MR group. Moreover, weight gain was significantly higher in patients who were given both gliclazide MR and rosiglitazone (5.5 ± 0.8 kg; p < 0.001). The rate of patients who achieved FPG < 126 mg/dL was similar in the three groups, but the proportion of patients with HbA1c levels < 7% was significantly lower (p < 0.001) in the metformin-rosiglitazone group. Figure 2 shows the effectiveness of the three drugs in reducing plasma glucose levels.

Tolerability

Metformin, gliclazide MR and rosiglitazone were well tolerated. As monotherapy, symptomatic hypoglycemia was reported by 2 of 40 (5%) of the gliclazide MR-treated patients, but by none of those that used metformin or rosiglitazone. During combination therapy, symptomatic hypoglycemia occurred in 5 of 65 (7.7%) patients treated with metformin and gliclazide MR, in 3 of 30 (10%) subjects who were given rosiglitazone plus gliclazide MR, and in only 1 (3.3%) of those who used metformin and rosiglitazone. The hypoglycemic episodes were mild, only happened in patients in use of 90 mg/day of gliclazide MR and did not recur after improvement of dietary habits and/or dose reduction to 60 mg/day of gliclazide MR. GI side-effects were more frequent in patients treated with metformin, both in monotherapy (11.6% versus 2.5% with gliclazide MR and 4% with rosiglitazone) and in combination therapy (12.3% with metformin and gliclazide MR, 10% with metformin plus rosiglitazone, and 3.3% with gliclazide MR and rosiglitazone). Ankle edema was only found in patients who received rosiglitazone (8% in monotherapy, 10% with gliclazide MR and rosiglitazone, and
6.6% with metformin plus rosiglitazone). No cases of myocardium infarction or cardiovascular death was observed during the first 24 weeks of treatment. Pulmonary edema was diagnosed in 1 of 30 patients (3.3%) treated with rosiglitazone alone by Week 20.

The rate of patients who discontinued monotherapy due to side-effects was comparable for the three drugs: 1/40 (2.5%) with gliclazide MR (skin rash), 3/60 (5%) with metformin (GI side-effects), and 2/25 (8%) with rosiglitazone (pulmonary edema, ankle edema, and weight gain). Discontinuation was not found in patients who were given combination therapy.

**Figure 1.** Comparative efficacy of monotherapy with metformin, gliclazide MR or rosiglitazone in the reduction of HbA1c at Weeks 12, 16 and 24.

### DISCUSSION

Different studies have shown that metformin, sulphonylureas and TZDs provide similar reductions in HbA1c (4,29-31). However, there is evidence that long-term durability of glycemic control would be higher with TZDs. Indeed, the ADOPT study has shown a cumulative incidence of monotherapy failure at five years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (31). Nevertheless, the most recent consensus statement for the management of type 2 diabetes from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends metformin, due to its greater safety, as the best drug to be used together with lifestyle changes at the beginning of treatment (7).

Most patients with type 2 diabetes will eventually require the combination of two or more drugs with different mechanisms of action to achieve an appropriate glycemic control (25-27). Different regimens have been proposed, but the most commonly used is metformin combined with a sulphonylurea (26,32,33). The rationale for the combination therapy with metformin and rosiglitazone or pioglitazone would be the fact that these drugs, despite being insulin sensitizers, target insulin resistance through different and complementary mechanisms (34,35). Indeed, whereas metformin has a stronger effect to suppress hepatic glucose output, TZDs have a stronger effect to increase peripheral glucose disposal (27,34,35). However, this therapy does not directly increase insulin secretion that is impaired in type 2 diabetes (3,26). Conversely, the co-administration of a sulphonylurea with an insulin sensitizer enables both reduction of insulin resistance and stimulation of...
### Table 3. Comparison of the effect of 24-week monotherapy on biochemical parameters and body weight

<table>
<thead>
<tr>
<th></th>
<th>Metformin Group (n = 60)</th>
<th>Gliclazide MR Group (n = 40)</th>
<th>Rosiglitazone Group (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in weight (kg)</td>
<td>-4.2 ± 0.9</td>
<td>4.0 ± 1.3</td>
<td>3.2 ± 0.8</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean reduction in FPG (%)</td>
<td>33.3 ± 4.5</td>
<td>34.0 ± 6.8</td>
<td>32.1 ± 7.2</td>
<td>0.945</td>
</tr>
<tr>
<td>Mean reduction in PPG (%)</td>
<td>32.0 ± 5.5</td>
<td>33.3 ± 6.8</td>
<td>30.8 ± 4.7</td>
<td>0.091</td>
</tr>
<tr>
<td>Mean reduction in HbA1c (%)</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.2</td>
<td>0.9 ± 0.4</td>
<td>0.088</td>
</tr>
<tr>
<td>Mean change in total cholesterol (%)</td>
<td>-7.7 ± 2.2</td>
<td>-6.2 ± 2.5</td>
<td>10.2 ± 3.6</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Rate of patients with FPG &lt; 126 mg/dL (%)</td>
<td>40</td>
<td>47</td>
<td>38</td>
<td>0.720</td>
</tr>
<tr>
<td>Rate of patients with HbA1c &lt; 7% (%)</td>
<td>27</td>
<td>30</td>
<td>25</td>
<td>0.956</td>
</tr>
<tr>
<td>Mean increase in HDL-cholesterol (%)</td>
<td>6.6 ± 0.9</td>
<td>6.4 ± 0.7</td>
<td>6.6 ± 0.5</td>
<td>0.485</td>
</tr>
<tr>
<td>Mean change in LDL-cholesterol (%)</td>
<td>-8.5 ± 1.7</td>
<td>-6.4 ± 1.3</td>
<td>12.4 ± 2.8</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean change in triglycerides (%)</td>
<td>-9.4 ± 1.8</td>
<td>-6.3 ± 1.4</td>
<td>9.4 ± 2.5</td>
<td>&lt; 0.001¹</td>
</tr>
</tbody>
</table>

¹Metformin versus gliclazide MR and rosiglitazone; ²Metformin and gliclazide MR versus rosiglitazone. FPG = fasting plasma glucose; PPG = postprandial plasma glucose.

### Table 4. Comparison of the effect of 24-week combination therapy on biochemical parameters and body weight

<table>
<thead>
<tr>
<th></th>
<th>Metformin + gliclazide MR Group (n = 65)</th>
<th>Gliclazide MR + rosiglitazone Group (n = 30)</th>
<th>Metformin + rosiglitazone Group (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean increase in body weight (kg)</td>
<td>2.2 ± 0.3</td>
<td>5.5 ± 0.8</td>
<td>2.1 ± 0.7</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean reduction in FPG (%)</td>
<td>58.2 ± 5.3</td>
<td>55.4 ± 7.8</td>
<td>46.2 ± 4.7</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean reduction in LDL-cholesterol (%)</td>
<td>50.6 ± 4.2</td>
<td>48.2 ± 6.6</td>
<td>42.1 ± 5.3</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean reduction in HbA1c (%)</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Rate of patients with FPG &lt; 126 mg/dL (%)</td>
<td>62</td>
<td>58</td>
<td>52</td>
<td>0.734</td>
</tr>
<tr>
<td>Rate of patients with HbA1c &lt; 7% (%)</td>
<td>41.5</td>
<td>40</td>
<td>28</td>
<td>0.044²</td>
</tr>
<tr>
<td>Mean reduction in total cholesterol (%)</td>
<td>9.6 ± 1.5</td>
<td>3.2 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean increase in HDL-cholesterol (%)</td>
<td>6.6 ± 0.9</td>
<td>6.4 ± 0.7</td>
<td>6.6 ± 0.5</td>
<td>0.485</td>
</tr>
<tr>
<td>Mean reduction in LDL-cholesterol (%)</td>
<td>8.6 ± 1.4</td>
<td>4.2 ± 0.9</td>
<td>3.2 ± 0.8</td>
<td>&lt; 0.001¹</td>
</tr>
<tr>
<td>Mean reduction in triglycerides (%)</td>
<td>10.7 ± 1.8</td>
<td>5.7 ± 1.4</td>
<td>1.2 ± 0.4</td>
<td>&lt; 0.001¹</td>
</tr>
</tbody>
</table>

¹Gliclazide MR + rosiglitazone versus gliclazide MR + metformin and metformin + rosiglitazone; ²Metformin + rosiglitazone versus gliclazide MR + metformin and gliclazide MR + rosiglitazone. ³Gliclazide MR + metformin versus gliclazide MR + rosiglitazone and metformin + rosiglitazone. FPG = fasting plasma glucose; PPG = postprandial plasma glucose; GI = gastrointestinal.

**Figure 2.** Mean reduction of plasma glucose levels with metformin (MET), gliclazide MR (GLIC) and rosiglitazone (RGZ) as monotherapy or in combination. The mean reduction of FPG and PPG levels was significantly lower with MET + RGZ.
insulin secretion from pancreatic β-cells (5,8). In the UKPDS, the addition of metformin to a sulphonylurea increased the proportion of patients achieving HbA1c levels of less than 7% at 3 years from 21% to 33% (36).

In the present study, we found that therapy for 24 weeks with metformin, gliclazide MR or rosiglitazone as monotherapy was equally effective in improving glycemic control, a result that supports data from previous studies (3-7,31). However, at Week 12, the improvement of glycemic control was less pronounced with rosiglitazone, suggesting a slower effect of this drug. This finding is consistent with the observation that the glucose-lowering effect of TZDs is usually more gradual, and may take more than three months to reach its maximum efficacy (22-24,27). Furthermore, rosiglitazone-treated patients had higher levels of total cholesterol, LDL-c and triglycerides. It has been shown that, whereas pioglitazone usually produces a fall in triglycerides of at least 10%-20%, with little change in LDL-c, rosiglitazone tends to increase both LDL-c and triglycerides levels (21-25,37). By contrast, the effects of metformin on lipid profile are modest, but usually favorable (21,38).

On the assessment of combined therapies at Week 24 we found that the metformin-rosiglitazone combination was the less effective option in improving glycemic control (p < 0.001) whereas the other treatments were equally efficient. Additionally, the improvement of lipid profile was significantly better (p < 0.001) in the metformin-gliclazide MR group. Similar results were reported by Garber and cols. (39), who compared the combination of another sulphonylurea (glibenclamide) or rosiglitazone with metformin. In that study, more patients receiving metformin-glibenclamide attained a HbA1c concentration < 7.0% than did those in the metformin plus rosiglitazone group (60% versus 47%) and had fasting plasma glucose levels < 126 mg/dL at week 24 (34 versus 25%). In the study by Derosa and cols. (40), the improvement of lipid profile was also significantly greater in the metformin-glimepiride group whereas the reduction of plasma glucose and HbA1c was similar in patients treated with metformin plus glimepiride or metformin plus rosiglitazone. By contrast, in the RECORD study (41) patients treated with rosiglitazone plus metformin or a sulphonylurea achieved significantly lower values of HbA1c as compared to those that received the combination of metformin with a sulphonylurea, but they developed higher weight and LDL-c levels.

In the current study, the three drugs evaluated were well tolerated, either in monotherapy or in combination. While GI side-effects were more frequent among metformin-treated patients, symptomatic hypoglycemia and ankle edema were more prevalent with gliclazide MR and rosiglitazone, respectively. In clinical trials, the incidence of TZDs-associated edema varied from about 3.0% to 7.5%, compared to 1.0% to 2.5% with placebo or other oral glucose-lowering agents (24). Weight gain induced by TZDs is usually modest (mean of 3.6 kg) but may be excessive leading to discontinuation of treatment (42). TZDs are also associated with an increased incidence of fractures in women and perhaps in men (7,41,43). Large trials, such as RECORD (41) and PROactive (42), showed that the use of TZDs results in a twofold increased risk for congestive heart failure (41,42). Moreover, two meta-analyses have suggested a 30%-40% relative increase in risk for myocardium infarction in type 2 diabetic patients treated with rosiglitazone (44,45). In the RECORD study, a non-statistically significant increased risk for myocardium infarction was noted in the rosiglitazone group (HR 1.14, 0.80-1.63) (41). However, low event rates might have precluded the statistical confirmation of significant risk, if present. Also, rosiglitazone was associated with higher LDL-c levels leading to an increased use of statins in the rosiglitazone group which might have reduced the incidence of cardiovascular events (46). Conversely, a meta-analysis of 19 randomized trials has indicated that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with type 2 diabetes (47). In our series, there were no cases of myocardium infarction or deaths related to CVD. However, pulmonary edema developed in 1 of the 30 patients (3.3%) who received rosiglitazone monotherapy. The joint consensus statement of ADA and EASD on the medical management of hyperglycemia in type 2 diabetes considers TZDs as less well-validated therapies and, as evidence currently favors pioglitazone, recommends the use of pioglitazone instead of rosiglitazone, when prescribing TZD therapy (7).

In conclusion, our data demonstrated that, as monotherapy metformin, rosiglitazone and gliclazide MR were equally effective in improving glycemic control whereas only rosiglitazone therapy was not associated with improvement of the lipid profile. Moreover, the combination of metformin plus gliclazide MR provided a greater improvement of glycemic control and lipid
profile in comparison to the metformin–rosiglitazone group, as well as a more pronounced improvement of lipid profile as compared to the gliclazide MR/rosiglitazone combination therapy.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES


