Comparative study between Metformin, Glibenclamide and their combination in newly diagnosed diabetic (type II) patients in Hawler City


* Department of clinical pharmacy, College of pharmacy, Hawler medical university
** Department of clinical pharmacy, College of pharmacy, university of Baghdad

Keywords, metformin, glibenclamide, diabetes

The abstract:

Diabetes is a chronic disease characterized by an increased level of blood glucose, usually caused by a decrease in the release of insulin (pancreatic β-cells) or an inadequate response to the insulin produced. The treatment of type 2 diabetes aims to control blood glucose levels and manage the disease. The study aimed to compare the efficacy and safety of metformin, glibenclamide, and their combination in the treatment of newly diagnosed type II diabetes patients in Hawler City.

Methods:

A total of 90 patients with type 2 diabetes were enrolled in the study. They were divided into three groups: group A (control group) received glibenclamide (glibenclamide), group B received metformin (metformin), and group C received a combination of glibenclamide and metformin. The treatment was given for 8 weeks.

Results:

The results showed that the combination group had the lowest mean fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) levels compared to the control and single drug groups. The mean hemoglobin A1C (HbA1c) level was also lower in the combination group. No significant differences were observed in the lipid profile between the groups.

Conclusion:

The combination of metformin and glibenclamide was more effective in controlling blood glucose levels and had a better safety profile compared to the single drugs. This warrants further research to confirm these findings.
Abstract:

Type 2 diabetes mellitus is a complex progressive disorder characterized by impaired insulin sensitivity, reduced insulin secretion and progressive failure of pancreatic β−cells. Type 2 diabetes therapies are initiated with lifestyle changes (diet, exercise) and pharmacologic agents, including oral antidiabetic drug, among them: sulphonylurea (glibenclamide), Biguanide (metformin) and combination of them.

The objective of this study is to compare the efficacy of the drugs, both as monotherapy and in combination, and discussed evidence – based treatment.

Forty patients with (FPG of 167.9±3.5mg/dl; PPG of 276.3±5.4mg/dl; HbAlc of 8.1±0.2%) were received metformin (500mg tid), and 15 patients with (FPG of 165.1±4.3; PPG of 273.6±5.5; HbAlc of 7.9±0.2) were received glibenclamide (5mg once daily) monotherapy, 35 patients with (FPG of 179±4.1; PPG of 304.4±5.6; HbAlc of 7.9±0.1) were received glibenclamide/metformin (2.5mg/500mg bid) as combination therapy. Blood samples were withdrawn from the patients at pretreatment, then monthly for three months. After 3 months of treatment, patients who received glibenclamide/metformin combination (2.5/500mg) had greater reductions in FPG, PPG and HbAlc (-70.6mg/dl, -125.3mg/dl, and -2.0% for glibenclamide/metformin combination, respectively, compared to metformin monotherapy where FPG, PPG and HbAlc saw reductions of -88.5mg/dl, -52.3mg/dl, and -0.8%.

Conclusion:

Our study suggests that the combination of glibenclamide and metformin is more effective in reducing FPG, PPG and HbAlc compared to metformin monotherapy.

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125.3mg/dl, and -2.0% respectively), compared with metformin (-48.8mg/dl, and -88.5mg/dl, -1.6% respectively), or glibenclamide (-52.3mg/dl, -63.5mg/dl, 0.8% respectively). Metformin and glibenclamide/metformin combination had approximately similar effect in reduction of total cholesterol, triglyceride, and low – density lipoprotein cholesterol, compared with glibenclamide alone which showed elevation.

Metformin significantly increased high density lipoprotein cholesterol whereas glibenclamide/metformin combination or glibenclamide alone did not show that, also metformin reduces body weight significantly in contrast to glibenclamide/metformin and glibenclamide alone (which is associated with weight gain).

Metformin monotherapy and glibenclamide/metformin combination both are effective as an initial treatment of newly diagnosed diabetic patients in Kurdistan region (Hawler city). These two strategies reduced plasma glucose and HbA1c significantly, and both have favorable effect on serum lipid profile, but only metformin had a significant reduction of body weight in diabetic patients.

Introduction:

Diabetes mellitus is a chronic disease that requires long-term medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications [1]. Diabetes is a serious, costly and increasingly common disease [2], and there is great interest in identifying and implementing interventions to prevent or delay its onset [3]. Typically, at the time of diabetes diagnosis, nearly 50% of B-cell function has been lost and less than 60% of normal insulin sensitivity is present [4].

Type II diabetes is a complex heterogeneous group of metabolic conditions characterized by increased levels of plasma glucose due to impaired insulin sensitivity, reduced insulin secretion and progressive failure of β-cells [5,6].

Several classes of oral antihyperglycemic agents are administered as monotherapy to ameliorate hyperglycemia, but due to the progressive nature of type 2 diabetes, some patients eventually require combination therapy [7]. These classes include among others sulfonylureas, biguanide and their combination.

Aims of the study are:

1 - To investigate the efficacy of metformin, glibenclamide and their combination in improving fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed type 2 diabetic patients.
To investigate the effects of metformin, glibenclamide and their combination on serum lipid profile body weight and body mass index (BMI) in newly diagnosed type2 diabetic patients.

Patients and methods:
This study was conducted during the period from the 15th November 2009 till the 25th May 2010, which was carried out in Layla Qassem Diabetic Center and many outpatient clinics in Erbil city. The study included 90 newly diagnosed type 2 diabetic patients to be treated with oral antidiabetic agents and 30 healthy individuals without drug treatment as a control group. Full informations were taken by a questionnaire paper. Our subjects were divided into four groups:

Group A patients:
Includes forty patients, 22 women and 18 men ranging 30–70 years (mean ± SEM, 49.2 ± 0.8) taking metformin 500mg (glucophage, Merk serono) three times daily as antidiabetic drug.

Group B patients:
Includes thirty five patients, 19 women and 16 men ranging 42–60 years (48.5±1.09) taking glibenclamide/metformin (2.5/500mg) (glucovance, Merk serono) two times daily as antidiabetic drug.

Group C patients:
Includes fifteen patients, 7 women and 8 men ranging 36–65 years (48±1.9) taking glibenclamide 5mg once daily as antidiabetic drug.

Venous blood (8 ml) was collected from each patient. It was drawn after overnight fasting by venipuncture under basal condition using tourniquet with vacationer system. 2 ml of blood was transferred into EDTA tube for HbA1c testing, and the remaining blood was left for 15 minute at room temperature to be clotted then centrifuged at 3000 rpm for 5 minute. Two milliliters of the plasma was allowed for FPG and lipid profile tests. Two milliliters of venous blood was also collected after 2 hour of a meal for postprandial test.

Parameters used for analysis involved:
Estimation of plasma Glucose (fasting plasma glucose and postprandial blood glucose)\(^8\); glycosylated hemoglobin (HbA1c)\(^9\); serum Total cholesterol\(^{10, 11}\); serum Triglycerides\(^{12, 13}\); serum HDL-c\(^{14}\); serum LDL-c\(^{15}\) and estimation of Body mass index.

Statistical analysis:
Data were prepared as mean ± standard error of mean (SEM) paired t-test were used for statistical analysis and p-value < 0.05 was considered significance.
Results:

Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 1500 mg of metformin daily for 3 months shown in Table-1. Each value represented the mean ± standard error. Number of patients were 40.

<table>
<thead>
<tr>
<th>Month treatment</th>
<th>FPG mg/dl</th>
<th>PPG mg/dl</th>
<th>HbA1c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>167.9±3.5</td>
<td>276.3±5.4</td>
<td>8.1±0.2</td>
</tr>
<tr>
<td>After 1 month</td>
<td>143.6*±3.1</td>
<td>231.4*±4.4</td>
<td>7.7±0.2</td>
</tr>
<tr>
<td>After 2 month</td>
<td>126.9*±2.2</td>
<td>208.9*±4.3</td>
<td>7.0*±0.2</td>
</tr>
<tr>
<td>After 3 month</td>
<td>119.1*±2.0</td>
<td>187.8*±3.5</td>
<td>6.5*±0.1</td>
</tr>
</tbody>
</table>

Table-1: FPG, PPG, HbA1c for patients received metformin (Group A)
Values are expressed by mean ± SEM
*P< 0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index (BMI) of diabetic patients treated with 1500 mg daily dose of metformin for 3 months (table-2).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>BW kg</th>
<th>BMI kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>83.8±2.1</td>
<td>31.9±0.8</td>
</tr>
<tr>
<td>After 1 month</td>
<td>83.2±2.1</td>
<td>31.6±0.8</td>
</tr>
<tr>
<td>After 2 month</td>
<td>82.5*±2.0</td>
<td>31.4±0.8</td>
</tr>
<tr>
<td>After 3 month</td>
<td>81.6*±2.0</td>
<td>31.0±0.8</td>
</tr>
</tbody>
</table>

Table-2: Body weight and body mass index for patients received metformin (group-A).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol ; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 1500 mg daily dose of metformin for 3 months (table-3).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>TC mg/dl</th>
<th>TG mg/dl</th>
<th>HDL mg/dl</th>
<th>LDL mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>203.7±4.7</td>
<td>175.6±6.2</td>
<td>40±1.0</td>
<td>129.7±4.1</td>
</tr>
<tr>
<td>After 1 month</td>
<td>192*±3.0</td>
<td>171.2±7.3</td>
<td>40.1±0.8</td>
<td>119.1*±2.5</td>
</tr>
<tr>
<td>After 2 month</td>
<td>183.8*±2.3</td>
<td>166.3*±5.5</td>
<td>40.7±0.9</td>
<td>111.1*±1.9</td>
</tr>
<tr>
<td>After 3 month</td>
<td>177.5*±2.2</td>
<td>162.0*±5.7</td>
<td>43.2*±0.9</td>
<td>100.7*±2.1</td>
</tr>
</tbody>
</table>

Table-3: TC, TG, HDL-c and LDL-c for patients received metformin (group-A)
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.
Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 2.5 mg glibenclamide and 500mg metformin twice daily for 3 months. Number of patients were 35 (table-4).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>FPG mg/dl</th>
<th>PPG mg/dl</th>
<th>HbA1C %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>179.0±4.1</td>
<td>304.5±5.6</td>
<td>7.9±0.1</td>
</tr>
<tr>
<td>After 1 month</td>
<td>156.0*±4.6</td>
<td>248.1*±5.3</td>
<td>6.9*±0.1</td>
</tr>
<tr>
<td>After 2 month</td>
<td>127.8*±4.5</td>
<td>206.0*±5.3</td>
<td>6.6*±0.1</td>
</tr>
<tr>
<td>After 3 month</td>
<td>108.4*±1.8</td>
<td>179.1*±2.2</td>
<td>5.9*±0.1</td>
</tr>
</tbody>
</table>

Table-4: FPG, PPG and HbA1c for patients received glibenclamide / metformin combination (group B).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index of diabetic patients treated with 2.5 mg glibenclamide and 500mg metformin twice daily dose for 3 months (table-5).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>BW Kg</th>
<th>BMI kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>76.4±1.6</td>
<td>28.6±0.6</td>
</tr>
<tr>
<td>After 1 month</td>
<td>76.9±1.6</td>
<td>28.8±0.6</td>
</tr>
<tr>
<td>After 2 month</td>
<td>77.3*±1.6</td>
<td>29.0±0.6</td>
</tr>
<tr>
<td>After 3 month</td>
<td>77.4*±1.6</td>
<td>29.0±0.6</td>
</tr>
</tbody>
</table>

Table-5: Body weight and body mass index for patient received glibenclamide / metformin combination (group-B).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol ; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 2.5 mg of glibenclamide and 500mg metformin twice daily dose for 3 months (table-6).

<table>
<thead>
<tr>
<th>Month treatment</th>
<th>TC mg/dl</th>
<th>TG mg/dl</th>
<th>HDL mg/dl</th>
<th>LDL mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>204.5±3.5</td>
<td>170.1±6.7</td>
<td>41.4±0.9</td>
<td>130.7±3.1</td>
</tr>
<tr>
<td>After 1 month</td>
<td>189.2*±3.3</td>
<td>162.2±5.7</td>
<td>41.5±0.9</td>
<td>117.2*±2.8</td>
</tr>
<tr>
<td>After 2 month</td>
<td>186.2*±2.7</td>
<td>161.1*±3.2</td>
<td>42.0±0.6</td>
<td>113.0*±2.0</td>
</tr>
<tr>
<td>After 3 month</td>
<td>179.1*±1.7</td>
<td>157.2*±3.7</td>
<td>42.8*±0.6</td>
<td>103.5*±1.3</td>
</tr>
</tbody>
</table>

Table-6: TC, TG, HDL-c and LDL-c for patient received glibenclamide/metformin combination (group-B).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.
Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 5 mg of glibenclamide once daily for 3 months. Number of patients were 15 (table 7).

<table>
<thead>
<tr>
<th>Month treatment</th>
<th>FPG mg/dl</th>
<th>PPG mg/dl</th>
<th>HbA1c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>165.1±4.3</td>
<td>273.6±5.5</td>
<td>7.9±0.2</td>
</tr>
<tr>
<td>After 1 month</td>
<td>127.5±1.6</td>
<td>218.8±3.5</td>
<td>7.2±0.1</td>
</tr>
<tr>
<td>After 3 month</td>
<td>112.8±1.9</td>
<td>210.1±4.4</td>
<td>7.1±0.1</td>
</tr>
</tbody>
</table>

**Table-7:** FPG, PPG and HbA1c for patients received glibenclamide (group-C).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index of diabetic patients treated with 5 mg daily dose of glibenclamide for 3 months (table-8).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>BW Kg</th>
<th>BMI kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>69.7±1.8</td>
<td>25.8±0.9</td>
</tr>
<tr>
<td>After 1 month</td>
<td>70.4±1.8</td>
<td>26.1±0.9</td>
</tr>
<tr>
<td>After 3 month</td>
<td>71.4±1.7</td>
<td>26.5±0.9</td>
</tr>
</tbody>
</table>

**Table-8:** Body weight and body mass index for patients received glibenclamide (group-C).
Values are expressed by mean ± SEM
*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 5 mg daily dose of glibenclamide for 3 months (table-9).

<table>
<thead>
<tr>
<th>Month Treatment</th>
<th>TC mg/dl</th>
<th>TG mg/dl</th>
<th>HDL mg/dl</th>
<th>LDL mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>196.3±7.3</td>
<td>163.6±11.5</td>
<td>40.0±1.1</td>
<td>127.3±5.7</td>
</tr>
<tr>
<td>After 1 month</td>
<td>200.6±7.4</td>
<td>172.0±11.0</td>
<td>40.0±1.0</td>
<td>125.6±6.5</td>
</tr>
<tr>
<td>After 3 month</td>
<td>216.0±13.2</td>
<td>181.6±7.1</td>
<td>41.0±1.0</td>
<td>138.6±12.8</td>
</tr>
</tbody>
</table>

**Table-9:** TC, TG, HDL-c and LDL-c for patients received glibenclamide (group-C).
Values are expressed by mean ± SEM
*P<0.05 significant difference between treated and pretreated values.
Table-10: Values of FPG mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.

Different letters represent significance in values.
Table-11: Values of PPG mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.
Table-12: Values of HBA1c (%) mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.

Discussion:
Many specialists recommended the use of metformin as first drug of choice in newly diagnosed diabetic patients in Hawler city, strategy which was in parallel to the strategy used in the treatment of diabetes mellitus in other countries [16]. In order to investigate the advantage of this strategy and to
compare the efficacy of metformin or glibenclamide and their combination, the present work was conducted. The present work was designated to compare the effect of metformin, glibenclamide and their combination on fasting plasma glucose, postprandial plasma glucose, glycemic control, body weight and body mass index, lipid profiles in newly diagnosed diabetic patients.

Metformin reduced FPG, PPG levels by 48.8 mg/dl and 88.5 mg/dl after 3 months of treatment respectively from the base line, with a percent reduction of 29%, 32%, respectively. Glibenclamide reduce FPG, PPG, levels by 52.3 mg/dl and 63.5 mg/dl after 3 months of treatment respectively from the base line, with a percent of reduction 31.6% and 23.2%, HbA1c was significantly achieved the recommended target after 3 months of treatment, so the change from the base line level was -1.6% for metformin and -0.8% for glibenclamide respectively with a percent reduction of 29% and 10.1% respectively. It was obvious from these results that metformin or glibenclamide reduced the FPG, PPG and HbA1c to about normal boarder values after 3 months of treatment. Similar results were observed by other workers used metformin or glibenclamide for the treatment of newly diagnosed diabetic patients [17, 18].

Diabetic patients who received metformin showed a significant reduction in the TC, TG and LDL-c values as compared to the pretreatment values. The HDL-c was significantly increased by 3.2 mg/dl after 3 months of treatment with a percent increase of 8%. These results were comparable to the results of other workers who demonstrated a reduction in bad lipids and an increase in good lipids after metformin therapy [19,20]. In contrast, diabetic patients receiving glibenclamide showed a significant increase in the TC, TG, and LDL-C values. However, HDL-C level was also increased by 1 mg/dl from base line after 3 months of treatment with a percent of elevation 2.5%. Several workers showed comparable results of glibenclamide on serum lipid profile of diabetic patients [21,22].

Patients administered metformin therapy had a significant decrease in body weight of 2.6kg from base line after 3 months of treatment, and percent reduction of 2.6 of body mass index, while patients administered glibenclamide had a significant increase in body weight of 1.7kg with a percent increase of 2.4% of body mass index. These results were comparable to that observed by others [23,24]. So the results of the present study suggested that metformin is an oral hypoglycemic drug which had a comparable efficacy to glibenclamide and it had a favorable effect on serum lipid profile and body weight.

Treatment with glibenclamide /metformin combination (2.5/500 mg) had resulted a greater reduction of FPG and PPG from base line as compared to the previous values of metformin or glibenclamide alone. However, HbA1c was reduced by 2.0 from base line with a percent reduction of 25.3%. This could
indicate that achieving the recommended target of HbA1c by a combination therapy produces greater improvements in glycaemic control.

Treatment with glibenclamide –metformin combination also showed a significant reduction of serum lipid profile in newly diagnosed diabetic patients. Significant reduction was observed in TC, TG and LDL-c. The HDL-c was significantly increased by 1.0 mg/dl only after 3 months with a percent increase of 1.3 %. These results were comparable to the values observed in metformin treated group, which could be indicated that in combination therapy, metformin still had the advantage of lowering bad cholesterol and increasing good lipid, even in the presence of glibenclamide [25,26].

Type II diabetes patients have a dual pathophysiologic defects, insulin resistance and progressive beta-cell dysfunction [27]. In combination therapy, metformin reduced the basal rate of hepatic glucose production [28], and increased glucose uptake by peripheral tissues [29], where as glibenclamide stimulate insulin secretion by the pancreatic β-cells [30], so these two agents were used to correct the dual defect of glucose in diabetic patients [7]. On the other hand the use of a single antihyperglycemic agent corrected only one of these defects, so the management of type 2 diabetes may be less than optimal with initial monotherapy [31].

Conclusion:
Metformin monotherapy and glibenclamide/metformin combination therapy both provide superior efficacy as an initial management of type 2 diabetes in kurdistan region. The two strategies improve fasting blood glucose, postparandial blood glucose and glycocelated hemoglobin significantly, and both have favorable effect on serum lipid profile. Combination treatment is more effective than either drug alone in improving glycemic control in type 2 diabetes.

References:
1 - American Diabetes Association (2008). Standards of Medical Care in Diabetes, Diabetes Care31:S12-S54


