Evaluation of Metformin + Sitagliptin versus Metformin + Glibenclamide on Glycemic Control in Iraqis Type 2 Diabetic Patients

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Abstract

Combination therapy with a dipeptidyl peptidase–4 inhibitor and metformin or metformin+glibenclamide results in substantial and additive glucose- lowering effects in Iraqis patients with type 2 diabetes mellitus. This study evaluated the glycemic control by using two groups of combinations of drugs metformin + glibenclamide and metformin + sitagliptin in Baghdad teaching hospital / medical city. 68 T2DM patients and 34 normal healthy individuals as control group were enrolled in this study and categorized in to two treatment groups. The group 1 (34 patients) received metformin 500 mg three times daily + glibenclamide 5 mg twice daily and the group 2 (34 patients) received metformin 500 mg three times daily + sitagliptin 100 mg once daily. From each patients 5 ml of blood was obtained by veinpuncture and the serum was sepa- rated and used for estimating plasma glucose level (FPG, PPG) and HbA1c. The mean fasting plasma glucose and postprandial plasma glucose significantly lower for group 2 patients for 3 and 6 months of treatment (129.02 ± 1.96 and 118.4 ± 1.33), (159.38 ± 4.72 and 123.88 ± 2.41 mg / dl) respectively for fasting plasma glucose and postprandial plasma glucose respectively than in group 1 patients (150.76 ± 3.97 and 127.79 ± 2.52) , (173.25 ± 7.99 respectively and 140.67 ± 4.66 mg / dl) for fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) respectively. The mean HbA1c % significantly lower for group 2 patients for 3 and 6 months of treatment (6.12 ± 0.091and 5.83 ± 0.083) respectively compared to group 1 patients (7.1 ± 0.63 and 6.81 ± 0.12 ). In conclusion, the combination of metformin + sitagliptin improved fasting plasma glucose, postprandial plasma glucose & HbA1c % in comparison with metformin + glibenclamide combination.

Key words: Sitagliptin, Metformin, Glibenclamide, Type 2 Diabetic Patients.

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Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders. Although the prevalence of type 2 DM increases with age, the disorder is increasingly being recognized in adolescence. Much of the increase in adolescent type 2 DM is related to an increase in adiposity and sedentary lifestyle, in addition to an inheritable predisposition. The increase in insulin resistance with weight gain is directly related to the amount of visceral adipose tissue. The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger). HbA1c measurements are the gold standard for following long-term glycemic control for the previous 2 to 3 months. Until 1995, only two options for pharmacologic treatment were available for patients with diabetes: sulfonylurea (for type 2 DM only) and insulin (for type 1 or 2). Since 1995, a number of new oral agents, injectables, and insulins have been introduced in therapy. Currently, six classes of oral agents are approved for the treatment of type 2 diabetes: α-glucosidase inhibitors, biguanides, meglitinides, peroxisome proliferator-activated receptor B-agonists (which are also commonly identified as thiazolidinediones [TZDs] or glitazones), DPP-IV inhibitors, and sulfonylurea. It is now known that two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin-releasing peptide (GIP), are responsible for more than 90% of the increased insulin secretion seen in response to an oral glucose load. In patients with type 2 diabetes GLP-1 levels are reduced whereas GIP levels are increased. Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase – 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal by preventing GLP-1 and GIP inactivation, the are able to the increase secretion of insulin and suppress the release of glucagons by pancreas. The aim of this study is to evaluate effects of combination of metformin + sitagliptin versus the effects of combination of metformin + glibenclamide on fasting plasma glucose, postprandial plasma glucose and HbA1c percentage in Iraqis type 2 diabetic patients.

Subjects and Methods

This study was carried out at Baghdad teaching hospital / Medical city & the National Diabetes Center for Treatment and Research at Al-mustansuriyah University and the private clinic of consultant physician during the period of July 2011-March 2012 .The study was conducted on ( 100 ) Iraqi type 2 diabetics only 68 patients completed the course of study successfully . These patients were recruited into the following groups : 

Group (1) : Includes 34 patients tested at zero time and after 3 months and 6 months. The patients were already treated by metformin 500mg three times daily & glibenclamide 5 mg twice daily.

Group (2) : Includes 34 patients tested at zero time and after 3 months and 6 months . The patients were previously treated by metformin 500mg three times daily and sitagliptin 100 mg once daily 3-6 months before start the study and they continue on this regime of treatment . The age of patients for group (1) ranged from 40 – 59 years (52.5 ± 0.86 ), of them 20 patients (58.8 %) were male and 14 patients (41.2 %) were female .The age of patients for group (2) ranged from 44 – 59 (52.44 ± 0.9),of them 20 patients (58.8 %) were male and 14 patients (41.2 %) were female.

Diagnosis was made by consultant endocrinologist; for patients as having T2DM depending on patients history, clinical examination laboratory investigations and vital signs. For the purpose of comparison ,34 control subjects were enrolled. The age of control for group (3) ranged from 44 – 59 (52.44 ± 0.9),of them 20 patients (58.8 %) were male and 14 patients (41.2 %) were female. Patients were excluded from this study as having the following criteria : CNS disease, renal dysfunctions, liver dysfunction, pregnancy with diabetes, concomitant endocrine disease & inflammatory Disease.

Collection of blood sample

From each patients ,5 ml of blood was obtained by vein puncture, for fasting and HbA1c. Another 5 ml was withdrawn for postprandial plasma glucose. The blood sample was divided into two aliquots; 2 and 3 ml . The first aliquots was dispended in tube containing ethylene diamine tetracetic acid ( EDTA ) (1.5 mg /ml ). This blood was processed in less than three hours and was used for HbA1c estimation and other portion ( 3 ml ) was dispensed in a plane tube and left for an hour.
to clot at room temperature then, it was centrifuged at 3000 rpm for 10 minutes to collect serum. The serum was separated and used for estimating plasma glucose level (FPG). By using an enzymatic colorimetric method with a commercially available kit for determination plasma glucose level and Bio-Rad VARIANT Hemoglobin A1c for determination HbA1c.

Results

Fasting plasma glucose (FPG)\(^9\)

The results showed significant reduction in fasting plasma glucose for both groups after 3 and 6 months of treatment as compared to 1\(^{st}\) reading. However, there is a significant decline for group 2 treated by metformin + sitagliptin compared to group 1 treated by metformin + glibenclamide (table.1 and fig 1).

<table>
<thead>
<tr>
<th>Duration months</th>
<th>Group 1 mg/dl</th>
<th>Group 2 mg/dl</th>
<th>Group3 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>173.97 ± 5.37(^a)</td>
<td>144.94 ± 3.25(^b)</td>
<td>100.11 ± 1.76</td>
</tr>
<tr>
<td>3</td>
<td>150.76 ±3.97(^ab)</td>
<td>129.02 ± 1.96(^abc)</td>
<td>96.02 ± 1.29</td>
</tr>
<tr>
<td>6</td>
<td>127.79 ±2.52(^ab)</td>
<td>118.4 ± 1.33(^abc)</td>
<td>94.50 ± 1.24</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard error of mean.

\(a\) significant difference (\(p < 0.05\)) in comparison with control group.
\(b\) significant difference (\(p < 0.05\)) between reading.
\(c\) significant difference (\(p < 0.05\)) between group 1 and 2.

Figure 1: Histogram showing effect of treatment with metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily (group 1) versus metformin 500 mg 3 times daily + sitagliptin 100 mg once daily (group 2) on fasting plasma glucose in patients with T2DM and control normal healthy individuals (group 3) after 1, 3 and 6 months of treatment. (n = 34 individuals for each group).

Postprandial plasma glucose (PPG)\(^9\)

Table 2 shows comparison between the effects of two types of treatment (metformin + glibenclamide and metformin + sitagliptin) on postprandial plasma glucose in patients with T2DM. There were a significant reductions in postprandial plasma glucose for both groups after 3 and 6 months of treatment as compared to 1\(^{st}\) reading. However, there was a significant decline for group 2 patients treated by metformin + sitagliptin compared to group 1 treated by metformin + glibenclamide.
Table 2: Effect of treatment with metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily (group 1) versus metformin 500 mg 3 times daily + sitagliptin 100 mg once daily (group 2) on postprandial plasma glucose PPG in patients with T2DM and control normal healthy individuals (group 3) after 1, 3 and 6 months of treatment. (n = 34 individuals for each group).

<table>
<thead>
<tr>
<th>Duration months</th>
<th>Group 1 mg/dl</th>
<th>Group 2 mg/dl</th>
<th>Group 3 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>203.26 ± 12.37a</td>
<td>186.05 ± 6.2ac</td>
<td>108.14 ± 1.34</td>
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<td>3</td>
<td>173.25 ± 7.99ab</td>
<td>159.38 ± 4.72abc</td>
<td>104.6 ± 1.19</td>
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<tr>
<td>6</td>
<td>140.67 ± 4.66ab</td>
<td>123.88 ± 2.41abc</td>
<td>96.29 ± 2.41</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard error of mean.

a significant difference (p < 0.05) in comparison with control group.

b significant difference (p < 0.05) between reading.

c significant difference (p < 0.05) between group 1 and 2.

Figure 2: Histogram showing effect of treatment with metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily (group 1) versus group 2 metformin 500 mg 3 times daily + sitagliptin 100 mg once daily (group 2) on PPG in patients with T2DM and group 3 control normal healthy individuals (group 3) after 1, 3 and 6 months of treatment. (n = 34 individuals for each group).

Glycosylated hemoglobin (HbA1c) Table 3 shows comparison between the effects of two groups of treatment (metformin + glibenclamide and metformin + sitagliptin) on HbA1c in patients with T2DM. There were a significant reductions in HbA1c for both groups after 3 and 6 months of treatment as compared to 1st reading. However, there were a significant decline for group 2 patients treated by metformin + sitagliptin compared to group 1 treated by metformin + glibenclamide after 3 and 6 months of treatment.
Table 3: Effect of treatment with metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily (group 1) versus group 2 metformin 500 mg 3 times daily + sitagliptin 100 mg once daily (group 2) on HbA1c in patients with T2DM and control normal healthy individuals group (3) after 1, 3 and 6 months of treatment. (n = 34 individuals for each group)

<table>
<thead>
<tr>
<th>Duration/ months</th>
<th>Group 1 (% HbA1c)</th>
<th>Group 2 (% HbA1c)</th>
<th>Group 3 (% HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.38 ± 0.14a</td>
<td>6.32 ± 0.09ac</td>
<td>5.33 ± 0.83</td>
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<tr>
<td>3</td>
<td>7.10 ± 0.63a</td>
<td>6.12 ± 0.09ac</td>
<td>5.31 ± 0.86</td>
</tr>
<tr>
<td>6</td>
<td>6.81 ± 0.12a</td>
<td>5.83 ± 0.08abc</td>
<td>5.01 ± 0.04</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard error of mean.
a significant difference (p < 0.05) in comparison with control group.
b significant difference (p < 0.05) between reading.
c significant different (p < 0.05) between group 1 and 2.

Discussion

The epidemic of type 2 diabetes and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority (11,12). Intensive glycemic management resulting in lower A1C levels has also been shown to have beneficial effect on cardiovascular disease (CVD) complication in type 1 diabetes (13,14); however, current studies failed to demonstrate a beneficial effect of intensive diabetic therapy on CVD in type 2 diabetes (15,16). The development of new classes of blood glucose-lowering medication to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylurea, and metformin, has increased in number of treatment options available to practitioners and patients has heightened uncertainty regarding the most appropriate means of treating this widespread disease (17). GLP-1 and glucose-dependent insulino tropic polypeptide (GPI), the main insulino tropic peptide of intestinal origin (incretins), are rapidly degraded by dipeptidyl peptidase four (DPP-4). DPP-4 is a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells (18). The 1st oral DPP-4 inhibitor, sitagliptin was approved by the Food and Drug Administration in October 2006 for use as monotherapy or in combination with metformin or TZDs. Another DPP-4 inhibitor, vildagliptin, was approved in Europe in February 2008, and several other compounds are under development. In clinical trial
performed to date, DPP-4 inhibitors lower A1C levels by 0.6 – 0.9 percentage points and are weight neutral and relatively well tolerated (19,20). They don’t cause hypoglycemia when used as monotherapy. A fixed-dose combination pill with metformin is available. Our results regarding plasma glucose and glycosylated hemoglobin (HbA1c) indicate that there was a successful improvement in plasma glucose levels and HbA1c after treatment courses of 3 and 6 months with metformin 500 mg three times daily + glibenclamide 5 mg twice daily and combination of metformin 500 mg three times daily + sitagliptin 100 mg once daily as was shown in tables 1-3; values were improved significantly after treatment with the above mentioned drugs. However, this improvement was not enough to reach that of normal healthy individual values, in other words, there were partial improvements observed by these drugs. Accordingly, and based on the comparison of the treatment groups with that of control group that continue for the same treatment period, we conclude that combination of metformin + sitagliptin significantly reduced the values of FPG, PPG and HbA1c after 3 and 6 months and improve plasma glucose level and HbA1c percentage compared to combination of metformin + glibenclamide. This might due to the additive effect of these two drugs i.e. metformin + sitagliptin. These results were in agreement with other results that also indicate effectiveness of additive effect of metformin and sitagliptin (21). The incretin hormones play a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying and reducing appetite and food intake (22-25). Both incretin hormones are rapidly degraded and removed from circulation by the enzyme dipeptidyl peptidase-4 (DPP-4) (26,27). Therefore, there is considerable interest in enhancing incretin action for treatment of type 2 diabetes. Sitagliptin, a selective DPP-4 inhibitor, reduces both fasting and postprandial plasma glucose presumably by inhibiting the inactivation of GLP-1 and GIP, thereby prolonging their duration of action on pancreatic islets (28,29). Also, the complementary combination therapy with sitagliptin–metformin lower glucose via enhancement of insulin secretion, suppression of glucagon secretion, and insulin sensitization. Use of this combination in diabetes management will provide a greater degree of glycosylated hemoglobin – lowering than that seen with use of either drug as monotherapy (22). In clinical trials, the DPP-4 inhibitor, sitagliptin, improved fasting and postprandial glycaemic control and measures of β-cell function in patients with type 2 diabetes, with minimal effects on measures of insulin resistance/sensitivity (30,31). Metformin has been found to increase GLP-1 levels in humans (32,33). Sulfonylurea have the advantage of being quite effective in blood glucose lowering, with an almost instant onset of the effect after start of therapy. Drops in HbA1c of 1–2% can be expected as a mean, with the higher the baseline HbA1c, the bigger the drop. Additive effects are seen when Sulfonylurea are combined with metformin, and the different mechanisms of action of these two agents – one stimulating insulin secretion, the other increasing insulin sensitivity – make them the obvious couple in the dual disease that is type 2 diabetes (34). The success story of this combination can be seen in many countries where this combination is the standard treatment in type2 diabetes. Suggestions that these drugs ultimately lead to faster beta-cell failure (an observation already made in the 1970s) have not altered their popularity (34). Because Sulfonylurea (SUs) have been used for so many years, their safety profile and side effects are well known. They increase insulin secretion by binding to a receptor on the surface of the pancreatic beta-cell, resulting in a glucose-independent insulin release. Their mechanism of action also implicates that Sulfonylurea therapy will ultimately fail because of B-cell failure. The main disadvantage of Sulfonylurea is the risk of hypoglycaemia, which rises with advanced age, poor nutrition, alcohol consumption, liver or kidney disease and polypathy (35) and is higher than with other oral medications (36). This is a class effect, but differences between different products have been described (37-39). Another class effect of SUs is that their use leads to weight gain, typically 1–4 kg with stabilization after about six months. (40) Here again, data are somewhat different between the products. (41,42). SUs have a neutral effect on lipid profile or blood pressure and all current SUs – in contrast to the older products, where worrying reports on cardiovascular mortality abound – are neutral to the heart. Most SUs are renally cleared and dose adaptations will be needed in the case of renal insufficiency. Therefore, it makes sense to choose SUs as the next step when metformin is not enough, but care should be taken in older patients because of the risk of hypoglycaemia. To justify its high cost, Sitagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function (43) and preferably used in combination with Metformin in order to
achieve the maximum reduction in HbA1c.\(^\text{44}\) All recent clinical trials hint to the benefit of the early use of sitagliptin, alone or in combination, of any antidiabetic medication. More specifically, GLP-1 or DDP4 inhibitors, have their maximum effect observed when the diabetic process is in its early manifestations.\(^\text{45}\) Also our study showed that good patients educations and instructions given the workers to the patients are of great value in controlling the fasting plasma glucose, postprandial plasma glucose and HbA1c after the 1st reading.

References


