Evaluation of Hypoglycaemic Effects of Dipeptidyl Peptidase–4 Inhibitors and Biguanide on Type-2 Diabetic subjects: A six months trial

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Author’s Contribution

1,4 Conception of study
1 Experimentation/Study conduction
1,4 Analysis/Interpretation/Discussion
4 Manuscript Writing
2,3,5,6 Critical Review
2,5 Facilitation and Material analysis

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Abstract

Objective: This trial was conducted to evaluate the effectiveness of oral hypoglycemic agents on diabetic control and biochemical parameters of known diabetic subjects.

Introduction: T2DM occurs due to abnormal metabolism of carbohydrates, proteins, and lipids leading to increased blood glucose characterized by polyuria and polydipsia due to relative deficiency or lack of insulin. Besides dietary control and insulin therapy, various oral hypoglycemic such as sulfonylurea biguanide, a thiazolidinedione, DPP–4 inhibitors, glucagon-like peptide inhibitors, and SGL2.

Material and Methods: This comparative trial was carried out on previously diagnosed type-2 diabetic subjects. This trial was conducted at health care centers of District Nowshehra viz. NMC Nowshehra, DHQ Hospital, Nowshehra, and ICS, Peshawar in collaboration with KMC and PIMC Peshawar, Khyber Pakhtunkhwa, Pakistan. A total of 200 known diabetic subjects were randomly recruited based on predetermined selection criteria and were split into two groups.

Results: Significant results (p < 0.05) were seen for glycemic control (FBS, RBS, HbA1C) in Group B as compared to Group A patients.

Keywords: Anti-diabetic, HbA1C, Sulfonylurea, DPP–4 Inhibitors
Introduction

Type-2 diabetes (T2DM) occurs due to abnormal metabolism of carbohydrates, proteins, and lipids leading to increased blood glucose characterized by polyuria and polydipsia due to relative deficiency or lack of insulin. T2DM, previously called NIDDM, account for up to 90–95% of diabetes. Type-2 diabetes is an islet paracrinopathy in which mutual connection exists between alpha cells (secrete glucagon) and beta cells (secrete insulin) is abolished which causes increased blood glucose level (hyperglycemia). Poor or deficient insulin production increases glycogen breakdown from glucose. In diabetes level of glucose is increased so more influx of glucose occurs than outflow. Abnormal functioning of islet cells is an important character of type-2. In type-2 diabetes increased hepatic glucose production occurs due to hypersecretion of glucagon. In obese type-2 diabetic patients insulin resistance is increased in the liver, muscles, adipose tissue, myocardium, overproduction, and underutilization of glucose occurs. According to the International Diabetes Federation (IDF) known patients of type-2 diabetes were 336 million in 2011 and this number will exceed up to 552 million by 2030.

Obesity and overweight are major risk factors for metabolic syndrome which is an important bunch of coronary heart disease (CAD) risk factors, like high blood pressure, diabetes mellitus, and dyslipidemia. A large number of research studies have revealed that subjects with deranged metabolism are at a high risk of future development of type-2 diabetes mellitus. T2DM is strongly associated with overweight and obesity. A positive link between body mass indexes (BMI), lipids, glucose, and blood pressure have been formerly reported. The death rate in diabetic individuals is 2 times more than individuals of the same age. In 2015 in the US diabetes is the 17th leading cause of death. Discovery of insulin in the 19th century comprised as a milestone for the control of glucose. Various oral hypoglycemic agents such as sulfonylurea, biguanide, thiazolidinedione, DPP-4 Inhibitors, glucagon-like peptide (GLP-1 Inhibitors), and SGL2 (Sodium Potassium Co-transport Inhibitors) are used to treat T2DM. DPP-4 inhibitors act by breaking down peptides like glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. DPP-4 inhibitors (discovered in 1966) are used as monotherapy or it can be used also with biguanide or with a thiazolidinedione. All drugs in this class are weight neutral. Common drugs of this class are Sitagliptin, Vildaglipitin, Saxagliptin, and Linagliptin.

Materials and Methods

This comparative study was carried out on previously diagnosed type-2 diabetic subjects. This study was conducted at health care centers of District Nowshera viz. Nowshera Medical Complex (NMC) Nowshera, District Head Quarter (DHQ) Hospital Nowshera, and Institute of Chemical Science (ICS), Peshawar in collaboration with Khyber Medical College and Pak International Medical College (PIMC), Peshawar, Khyber Pakhtunkhwa (KPK), Pakistan. A total of 200 known diabetic subjects were randomly recruited based on predetermined selection criteria and were divided into two groups. The first group (Group A) having 100 diabetic subjects was given DPP-4 inhibitor; Sitagliptin 50 mg two times a day alone for six (06) months while the second group (Group B) comprising of 100 patients were treated with a combination of DPP-4 inhibitor (Sitagliptin 50 mg 1 BD) and metformin in a dose of 500 mg two times a day. Venous blood samples were taken from all participants in both fasting (10–12 hour night long fast) and random (2 hours post-prandial) state. FBS, RBS, HbA1C, S. creatinine, blood urea, fasting lipid profile, and serum electrolytes were determined by spectrophotometric colorimetric methods using kits (procured from Elitech, Spain) at 03 and 06 months follow up. LDL-c was determined by Fried Wald’s formula. Inclusion criteria were that patients with T2DM of age 18years and above were included. T2DM patients on insulin, diabetic nephropathy, and retinopathy were excluded. The study was approved by the Ethical Board of the University of Peshawar. The data was analyzed by using SPPS software version 20.
Table 1 reveals the correlation of various demographic parameters and highly significant differences (p < 0.001) were found for age, BMI, SBP, and pulse respectively. Table 2 reveals the effects of the use of anti-diabetic drug DPP-4 inhibitors alone. The Mean ± SD results show that the fasting blood glucose level was notably changed (p<0.07) at the end of 6-month drug therapy. The data further reveals that the level of high-density lipoproteins in diabetic individuals rises again after the use of hypoglycemic agents (DPP-4 alone) for six months or more and the dissimilarity was outstanding (p<0.03). Similar findings were obtained for blood urea (p<0.07).

**Table 1: General Characteristics and Various Demographic Parameters (Means±SD) of Study Subjects**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (n=100)</th>
<th>Group B (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>52.50±11.80</td>
<td>59.00±15.70</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>32.25±6.68</td>
<td>27.94±5.21</td>
<td>0.000</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127.60±19.80</td>
<td>119.39±7.45</td>
<td>0.000</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.00±10.67</td>
<td>79.00±8.01</td>
<td>0.130</td>
</tr>
<tr>
<td>Pulse</td>
<td>90.00±2.80</td>
<td>85.00±9.52</td>
<td>0.000</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>68.00±3.22</td>
<td>67.00±1.33</td>
<td>0.471</td>
</tr>
</tbody>
</table>

Values are given as mean ±SD

**Table 2: The Effect of Use of Dipeptidyl Peptidase–4 (DPP–4) Inhibitors alone on Biochemical Parameters (Group A)**

<table>
<thead>
<tr>
<th>Biochemical Parameter</th>
<th>Baseline</th>
<th>03 Months</th>
<th>6 Months</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>189.33±82.95</td>
<td>142.67±47.86</td>
<td>113.33±40.86</td>
<td>0.07</td>
</tr>
<tr>
<td>RBS (mg/dL)</td>
<td>402.83±115.80</td>
<td>333.33±134.71</td>
<td>267.00±170.2</td>
<td>0.13</td>
</tr>
<tr>
<td>HbA1C</td>
<td>9.00±3.45</td>
<td>8.50±3.45</td>
<td>7.00±2.92</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Lipid Profile**

| Cholesterol (mg/dL)    | 211.67±38.68           | 182.50±19.42      | 147.50±81.59   | 0.11     |
| Triglycerides (mg/dL)  | 205.33±148.41          | 135.00±62.53      | 129.00±70.48   | 0.28     |
| HDL-c (mg/dL)         | 39.00±5.44             | 40.67±3.44        | 43.33±5.57     | 0.03     |
| LDL-c (mg/dL)         | 127.26±32.96           | 121.50±17.37      | 90.05±69.61    | 0.17     |

**Renal Profile**

| Urea (mg/dL)          | 50.33±16.50            | 33.33±14.12       | 36.67±4.17     | 0.07     |
| S. Creatinine (mg/dL) | 1.35±0.50              | 1.18±0.39         | 1.00±0.154     | 0.12     |

**Serum Electrolytes**

| Na⁺ (m mol/L)         | 138.00±5.65            | 136.00±0.00       | 139.33±4.50    | 0.66     |
| K⁺ (m mol/L)          | 4.41±0.57              | 3.75±1.66         | 4.28±0.57      | 0.69     |

Values are given as mean ±SD

Table 3 represents the effects of the use of combination drugs (DPP-4 inhibitor (Sitagliptin 50 mg 1 BD) and metformin in a dose of 500 mg two times a day) on biochemical parameters of diabetic subjects from baseline to 6 months duration of treatment. Mean±SD fasting blood sugar of diabetic individuals at the start, at after three (03) and six (06) months were found to be 145.40±56.92, 125.40±35.63 and 100.40±22.80 mg/dL respectively and insignificant change in the result (p>0.05) was observed for at the end of three months. However, the difference was highly outstanding (p<0.001) in the case of RBS after 6 months of combination drug therapy. The mean±SD Hba1c at the start after three and six months of treatment was found to be 8.25±1.91, 7.50±1.65, and 6.00±1.46, and the change was significant (p<0.05). A highly significant change (p < 0.00) was observed for serum total cholesterol HDL-c and LDL-c after six months duration of treatment with DPP-4 and metformin it was non-significant change (p>0.05) for TG. Mean±SD of blood urea of diabetic individuals at the start and following three and six months therapies were 32.80±5.49, 28.20±4.26, and 27.50±5.75 mg/dL respectively and insignificant change (p > 0.05) was noted. Similarly, mean±SD of serum creatinine at baseline, three and six months therapies were 1.20±0.31, 1.12±0.39, and 0.86±0.25 mg/dL, and significant difference (p<0.05) was noted. Contrast
results were obtained in the case of serum electrolytes especially serum potassium levels in the instant study.

**Table 3: The Effect of Use of Combination Drugs (Dipeptidyl Peptidase-4 Inhibitors + Metformin) (Group B)**

<table>
<thead>
<tr>
<th>Biochemical Parameter</th>
<th>Baseline</th>
<th>03 Months</th>
<th>p-values</th>
<th>6 Months</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>145.40±56.92</td>
<td>125.40±35.63</td>
<td>0.35</td>
<td>100.40±22.80</td>
<td>0.03</td>
</tr>
<tr>
<td>RBS (mg/dL)</td>
<td>308.30±75.50</td>
<td>249.80±66.03</td>
<td>0.08</td>
<td>186.50±66.51</td>
<td>0.00</td>
</tr>
<tr>
<td>Hb A1c</td>
<td>8.25±1.91</td>
<td>7.50±1.65</td>
<td>0.55</td>
<td>6.00±1.46</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Lipid Profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Total Cholesterol (mg/dL)</td>
<td>202.00±30.11</td>
<td>180.00±28.75</td>
<td>0.91</td>
<td>130.00±29.48</td>
<td>0.00</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>143.50±27.29</td>
<td>136.50±46.55</td>
<td>0.68</td>
<td>111.00±25.14</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>38.40±6.51</td>
<td>43.70±6.21</td>
<td>0.07</td>
<td>44.80±4.89</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>129.60±28.11</td>
<td>134.90±27.81</td>
<td>0.67</td>
<td>102.00±24.01</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Renal Profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>32.80±5.49</td>
<td>28.20±4.26</td>
<td>0.05</td>
<td>27.50±5.75</td>
<td>1.00</td>
</tr>
<tr>
<td>S. Creatinine (mg/dL)</td>
<td>01.20±0.31</td>
<td>01.12±0.39</td>
<td>0.61</td>
<td>0.86±0.25</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Serum Electrolytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺ (m mol/L)</td>
<td>135.70±1.56</td>
<td>137.80±2.89</td>
<td>0.05</td>
<td>138.90±3.63</td>
<td>0.02</td>
</tr>
<tr>
<td>K⁺ (m mol/L)</td>
<td>04.40±0.44</td>
<td>04.29±0.51</td>
<td>0.61</td>
<td>04.30±0.56</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Values are given as mean ±SD*

### Discussion

Dipeptidyl peptidase-4 inhibition decreases glucose levels and enhances beta cells’ function and decreases glucagon level, increased intact glucagon-like-peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). DPP-4 inhibitors control hyperglycemia in type-2 diabetes by affecting fasting as well as postprandial glucose. The results of our study are congruous with the studies mentioned above. Verities of DPP-4 inhibitors exist, and they decrease the HbA1C by ≈ 5–10 mmol/L in dual therapy (when added to metformin) and in monotherapy in studies over 6 months. Better glycemic control is attained by inactivation of the DPP4 enzyme that inhibits incretin hormones (GLP-1 and GIP). DPP-4 inhibition decreases glycemia sustainably. Furthermore, the reduction in glucagon after DPP-4 inhibition illustrated the chief mechanism supporting the improvement in glycaemia. The DPP-4 inhibitor varies in its structure and enzyme binding characters and pharmacokinetics. The effectiveness degree of DPP-4 inhibition varies between DPP-4 inhibitors however inhibition is sustained at 70 to 90% over 24 hours after drug administration. DPP-4 inhibitor is comprised of various types i.e. Alogliptin that affects improving insulin resistance when used in dual therapy with another hypoglycemic agent.

Dipeptidyl Peptidase-4 is a class of drugs that reduces the inactivation of GLP-1 and GIP which increases the synthesis of insulin and decreases glucagon release by pancreatic cells. Glycemic effectiveness is achieved when both DPP-4 and biguanide are used together. The same result was also noted by Sharma M et al., (2017) and Jain R (2015) respectively, and thus are in agreement with our results. Our observations regarding glycemic control by the use of DPP-4 as monotherapy was almost similar to that of sulfonylurea (as monotherapy) and is in accordance with the findings reported by Sharma M and coworkers (2017) however they instead of monotherapy used dual therapy (DPP-4 and Biguanide) and our results regarding dual therapy (DPP-4+Sulfonylurea) are almost comparable with the above.

According to our research on hypoglycemic agents used up to six months in monotherapy most effective drugs are sulfonylurea followed by DPP-4 regarding the reduction in HbA1C however, the result was carried out by Amir. Q and coworkers (2017) on hypoglycemic control show that using sulfonylurea class drugs over DPP-4 reduces Hb A1C but it has contradictory with the results that biguanide falls on the second number as compared to DPP-4. Effectiveness and protection of DPP-4 inhibitor combination treatment had been shown by numerous multicenter, non-specific, double-blind, placebo-controlled studies. Alike prior studies that manifested that combination treatment of DPP-4 inhibitor was secure and effective, the current survey indicated that the risks of severe hypoglycemia and death in patients dosed roughly with DPP-4 inhibitor in dual therapy were not different from those obtained with proper dosing of DPP-4 inhibitor as
monotherapy. To achieve much more effective results in controlling fasting and random blood glucose level and glycosylated hemoglobin we used combination therapy (dual therapy). Encouraging results were obtained in the case of dipeptidyl peptidase class along with sulfonylurea which reduces HbA1C concentration up to 2.25 from the results observed at baseline and the present results are in accordance with the observations reported by Amir Q and coworkers.

**Conclusion**

DPP-4 inhibition prevents hypoglycemia via increased glucagon counter-regulation through the incretin hormone glucose-dependent insulinotropic polypeptide. A combination of DPP-4 inhibitors with Biguanides has good glycemic control over DPP-4 inhibitors as monotherapy in obese T2DM with fewer chances of hypoglycemia.

**References**


