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# The Role of Hypoglycaemic Agent; Dipeptidyl Peptidase–4 and Its Relation with Biochemical Parameters in Patients With Type–2 Diabetes: A Three Months Trial

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## Abstract

**Objective:** This study was undertaken in order to find out the hypoglycemic control of DPP–4 on the diabetic patients and to evaluate the other related problems.

**Methodology:** A total of 320 type 2 diabetes patients were included in this study. They were treated with oral hypoglycemic drugs. Random as well as fasting blood samples were taken in all hygienic conditions. HbA1c, RBS, FBS, RFTs, serum electrolytes and lipid profiling was carried out by colorimetric methods using kits on Macro Lab 200. The kits were obtained from Elitech, Spain. Fried Wald's formula was used to determine LDL–c.

**Results:** FBS, HbA1C and urea were significantly different ($p < 0.05$) when compared with base line data while opposite results ($p > 0.05$) were obtained for RBS, serum total cholesterol, creatinine and TG and serum electrolytes.

**Conclusion:** Risk factors related to diabetes can be reduced by using anti–hyperglycemic agents (DPP–4) on regular basis for a period of three months or more.

**Key Words:** DPP–4, SGLT-1, T2DM, TZDs, ICS, KMC, Nowshehra.

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## Introduction

There is a raise in the incidence of type–2 diabetes mellitus (T2DM) each year in ageing population. It has been estimated that by 2040, there will be 615 million people suffering from T2DM.[1] T2DM causes micro and macrovascular complications. The risks of these complications, hospitalization, and death increase with the duration of the disease.[2] In addition, patients with diabetes have substantially higher medical care costs compared with those patients without diabetes[3]. Achieving glycemic control using pharmacotherapy is essential for the avoidance of disease progression and diabetes-related morbidities and mortalities. Furthermore, literature has associated good glycemic control with better clinical outcomes, including reduced risks of micro as well as macrovascular complications and progression.[4] Oral therapeutic management of diabetes becomes more challenging when patients develop diabetesrelated problems. First-line therapy, metformin is not recommended due to its association with lactic acidosis and cardiovascular complications. With the progression of diabetes, patients often require treatment intensification with second–line therapy. The major second–line treatment options include sulfonylureas, thiazolidinedione (TZDs), dipeptidyl peptidase–4 (DPP–4) inhibitors, glucagon–like peptide–1 (GLP–1) receptor agonists, and sodium glucose co-transporter–2 (SGLT–2) inhibitors. GLP–1 agonists are associated with gastrointestinal symptoms and SGLT–2

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inhibitors are not recommended because they causes moderate to severe kidney failure, and ketoacidosis. Although short-acting sulfonylurea are often used, but they often lead to hypoglycemia, as compared with other second–line agents when added to metformin mono therapy and therefore require cautious use by patients[5]. TZD causes edema, weight gain and bone fracture. The remaining class, DPP–4 inhibitors are acceptable for use in all stages and it is weight neutral and has low risk of hypoglycemia. Meta–analyses carried out on a number of clinical trials have shown that DPP–4 inhibitors have comparable efficacy as second–line therapies.[5,6] DPP–4 inhibitors including vildagliptin, sitagliptin and linagliptin lead to the reduction of sugar level mainly through inhibiting GLP–1 hydrolysis.[7,8] The present study was meant to determine the hypoglycemic control of DPP–4 on the diabetic patients of this region and to evaluate the other related problems.

## Materials and Methods

The present case–control study was carried out on diagnosed 320 type – 2 diabetic (T2DM) patients following predetermined selection criteria at health care centers of district Nowshehra viz. Qazi Hussain Medical Complex Nowshehra, District Headquarter Hospital (DHQ), Nowshehra, Khyber Pakhtunkhwa, Institute of Chemical Science (ICS), Peshawar in collaboration with Department of Biochemistry, Khyber Medical College (KMC), Peshawar, Khyber Pakhtunkhwa, Pakistan. The study was approved from the Advanced Study & Research Board, University of Peshawar and duration of the study was three months after the approval. They were treated for diabetes using anti-diabetic agent with standard protocol. After taking informed consent from the study participants approximately 5 mL blood was drawn from antecubital vein in 10-12 hour fasting condition with all aseptic measures. The blood sample was divided into two halves. One half was immediately transferred to EDTA tubes and the 2nd were centrifuged for 10 minutes at 500 rpm and the serum was taken in plastic capped bottles and stored till further analysis. For random blood sugar (RBS) random blood sample was also obtained. Fasting and random blood glucose was measured by using colorimetric methods using kits on Macrolab 200 (Bosch, Germany). DCA 2000 Analyzer (Bayer, USA) was used to measure HbA1C. Lipid profiling, renal function tests and serum electrolytes were determined using the kits procured from Elitech, Spain while LDL–c was estimated by Fried Wald's formula[9]. The data was analyzed for any statistically significant difference by using SPPS software version 20.

## Results

Table 1 represents the demographic parameters of the study population. The data reveals that BMI, age, pulse and SBP of type 2 diabetic subjects are highly significant ($p < 0.001$) when compared with normal subjects.

**Table 1: Demographic Parameters (Mean ±SD) of Study Population.**

| General Characteristics | | T2DM Subjects | Controls | p-value |
|---|---|---|---|---|
| BMI ( Kg/m$^2$ ) | | 32.25±6.68 | 27.94±5.21 | 0.000 |
| Age (Years) | | 52.50±11.80 | 59.00±15.70 | 0.002 |
| Pulse | | 90.00±2.80 | 85.00±9.52 | 0.000 |
| Heart Rate | | 68.00±3.22 | 67.00±1.33 | 0.471 |
| Blood Pressure | SBP (mm Hg) | 127.60±19.80 | 119.39±7.45 | 0.000 |
| | DBP (mm Hg) | 82.00±10.67 | 79.00±8.01 | 0.130 |

The effects of the use of DPP–4 on different biochemical parameters in known diabetic subjects recruited for the purpose study are depicted in Table–2. The Mean±SD results show that random blood sugar (RBS), serum total cholesterol, creatinine and triglycerides at baseline were found to be 402.83±115.80 mg/dL, 211.67±38.68 mg/dL, 1.36±0.50 mg/dL and 205.33±148.41 mg/dL respectively and there was an insignificant change ($p > 0.05$) when compared with results obtained after three (03) months

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

| Parameters | at Baseline | at 3rd Month | p–value |
|---|---|---|---|
| ***Biochemical Parameters*** | | | |
| HbA1C % | 9.50±3.25 | 8.00±3.45 | 0.02 |
| Fasting Blood Sugar (mg/dL) | 165.33±82.90 | 120.67±47.86 | 0.05 |
| Random Blood Sugar (mg/dL) | 402.83±115.80 | 335.33±134.71 | 0.36 |
| ***Renal Profile*** | | | |
| Urea (mg/dL) | 50.33±16.50 | 33.33±14.12 | 0.08 |
| Serum Creatinine (mg/dL) | 1.36±0.50 | 1.15±0.39 | 0.05 |
| ***Lipid Profile*** | | | |
| TG (mg/dL) | 205.33±148.41 | 135.00±62.53 | 0.31 |
| Total Cholesterol (mg/dL) | 211.67±38.68 | 182.50±19.42 | 0.13 |
| LDL–c (mg/dL) | 127.26±32.96 | 121.50±17.37 | 0.49 |
| HDL–c (mg/dL) | 34.00±5.44 | 40.67±3.44 | 0.04 |
| ***Serum Electrolytes*** | | | |
| $Na^+$ (m mol/L) | 138.00±5.65 | 135.00±0.00 | 0.40 |
| $K^+$ (m mol/L) | 04.41±0.57 | 03.75±1.66 | 0.37 |

treatment. Similar results were obtained for serum electrolytes. However at the end of treatment with DPP–4 alone these parameters were within the normal range and were dropped. The data suggested that the HDL–c level got raised after the use of hypoglycemic agents (DPP–4) alone over a period of three months or more and the difference was highly significant ($p$<0.05). Similar observations were made for other blood parameters such as fasting blood sugar (FBS), serum creatinine and blood urea (Table 2).

## Discussion

Our study was designed to determine the hypoglycemic control of DPP–4 on diabetic patients of this region and to evaluate the other related problems. The results of our study suggest that as compared to other oral hypoglycemic agents, which are mostly prescribed in combinations, leading to several unwanted complications, DPP–4 inhibitors alone are able to reduce blood sugar level, mortality and increase survival probability relative to use of non–DPP–4 inhibitors or no drugs. Other studies have also exhibited that DPP–4 inhibitors has better blood sugar lowering effect than the other hypoglycemic agents[10-12]. We compared the efficacy of DPP–4 inhibitors with that of sulfonylurea, biguanides, thiazoldendiones, and SGLT–2 agonists in mono therapy trial. Some randomized clinical trials have also explored the efficacy and safety of co–administering DPP–4 inhibitors. Fonseca *et al*., (2007)[13] used vildagliptin, and Hong *et al.,* (2012)[14] used sitagliptin; interestingly, both the studies reported significantly reduced risk of hypoglycemia relative to a placebo. While other studies, such as Lukashevich *et al.,* (2013)[15], Kothny *et al.,* (2013)[16], and Kozlovski (2013)[17] used vildagliptin; Barnett & colleagues (2012)[18] used saxagliptin; Arnolds *et al.,* (2010)[19] used sitagliptin; Yki–Jarvinen and co-researchers (2013)[20] used linagliptin; all of these investigators have reported neutral effects on hypoglycemia. Visboll and colleagues (2010) used sitagliptin and reported considerably increased risk of hypoglycemia.[21] These findings are consistent with the present study.

DPP–4 inhibition not only decreases blood glucose levels and enhances the beta cells' function but in addition, it also decreases glucagon level, and increases intact glucagon–like–peptide–1 (GLP–1) and glucose–dependent insulin tropic polypeptide (GIP). However, it also results in a reduced total GLP–1 and GIP. Dipeptidyl peptidase–4 inhibitors control glycaemia in type–2 diabetes through two mechanisms. They have an impact on not only the fasting glucose levels but also on postprandial glucose. Studies carried out over the period of 6 months have suggested that there is a variety of DPP–4 inhibitors[22], which decreases (glycated haemoglobin) HbA1c by ≈ 5–10 m mol/L in dual therapy i.e in combination with metformin and in monotherapy. A considerably better glycaemic control is achieved by inactivation of the incretin hormones such as glucagon–like peptide–1 and glucose–dependent insulinotropic polypeptide.[23] DPP–4 inhibitors decrease glycaemic levels for a substantial duration. Furthermore, the reductions of glucagon after DPP–4 inhibitors have exhibited important mechanisms underlying the improvement in glycaemia.[24] According to the present research study on hypoglycemic agents used for a period of three months or more in monotherapy; the most effective drugs in controlling blood glucose levels are sulfonylurea followed by DPP–4, than biguanide and least effective was thiozolidendiones on reducing HbA1c however the result carried out by Qaseem A *et al.(*2017) on hypoglycemic control shows that using sulfonylurea class drugs over GPP–4 reduces HbA1c are in agreement with our results but are contradictive with the results obtained after using biguanide and falls on the second number as compared to DPP–4[25].

## Conclusion

The study results suggest that DPP–4 inhibitors are alone capable enough to reduce blood sugar level, mortality and increase survival probability as compared to the non–DPP–4 inhibitors or no drugs. However, more comprehensive studies and trials are required to optimize the application of these DPP–4 inhibitors in the clinical world.

**RECOMMENDATIONS:**

Studies at larger scales shall be conducted in order to come to a conclusive strategy for adopting the appropriate measures for treating diabetes. Moreover need to educate people about the disorder and change their lifestyles and adopt the precautionary measures which will, in turn, decrease the socioeconomic burden.

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