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Original Research Article

Effects of either Sitagliptin or Pioglitazone Addition on Metformin in Patients with Uncontrolled Type 2 Diabetic Mellitus

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Abstract

Objective: Compare and study the use of metformin and DPP-4 inhibitors in conjunction with currently used combination treatments.

Materials and Methods: In this 16-week study, sitagliptin and pioglitazone were compared as add-on treatments for type 2 diabetes mellitus patients whose condition was not sufficiently controlled by metformin alone. In addition to metformin, 52 patients were randomly assigned to receive either sitagliptin 100 mg (group 1) or pioglitazone 30 mg (group 2). Change in HbA1c served as the main efficacy end objective. Changes in body weight, lipid profile, and fasting plasma glucose (FPG) were considered secondary end objectives. HbA1c significantly dropped in both groups.

Results: In neither group did the mean FPG reductions differ significantly from one another. In group 1, the mean body weight and body mass index significantly decreased, while the same variables significantly increased in group 2. High density lipoprotein (HDL-C) and triglyceride levels significantly dropped in both therapy groups, according to the reports.

Conclusion: The drug was well tolerated and did not cause any instances of hypoglycemia. It was determined that pioglitazone was not as effective or well tolerated as sitagliptin when added to metformin.

Keywords: DPP-4 inhibitors, diabetes mellitus, add-on therapy

Introduction

A chronic metabolic condition known as diabetes mellitus affects at least 171 million individuals globally. By 2030, this number is projected to more than double to 366 million

(76.4 million in India) [1]. If lifestyle changes alone are unable to slow the progression of the condition, oral antihyperglycemic medications are administered. The first-line diabetes medication that is most frequently prescribed globally is metformin. Due to the gradual deterioration of blood glucose control with the progression of the disease, combination therapy is typically required in the treatment of diabetes [2]. Metformin is frequently used in conjunction with pomglitazone when it is unable to control blood glucose on its own. In numerous randomised, placebo or active comparator-controlled studys lasting up to 3.5 years, the effectiveness of pioglitazone plus metformin combination therapy has been demonstrated in such individuals [3].

However, a number of unfavourable outcomes, such as edoema, weight gain, and osteoporosis, have been linked to thiazolidinediones (TZDs). Additionally, rosiglitazone has recently acquired a bad reputation due to its link to abnormal lipid profiles and myocardial infarction [4].

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor that is effective and highly selective when taken orally once daily for the treatment of type 2 diabetes. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are gut-derived peptides released into the bloodstream after meals, are active incretin hormones that are increased by DPP4 inhibitors. GLP-1 inhibits glucagon secretion in the presence of high glucose levels, hence reducing fasting glucose levels and minimising the postprandial rise in glucose levels. Both as a monotherapy and as an addition to currently available first-line anti-diabetic medications like metformin, sitagliptin has been authorised [5,6]. There haven't been many studies that contrast DPP-4 inhibitors and metformin with other well-known combo treatments for diabetes mellitus. Additionally, there is a lack of information on the impact of DPP-4 inhibitors on lipid profiles and treatment satisfaction.

In order to examine sitagliptin and pioglitazone as add-on therapies for patients with type 2 diabetes mellitus who were not satisfactorily managed by metformin alone, the current study was a randomised, parallel group study lasting 16 weeks.

Materials and Methods

From July 2021 to June 2022, the study was carried out at the Rama Medical College Hospital and Research Centre in Kanpur, Uttar Pradesh, in the Pharmacology Departments associated with the Department of Medicine. The institutional ethics committee gave its approval to the protocol.

All study participants provided their written informed permission. A computer-generated block randomization was used to enroll the patients and distribute them at random. Participants in the study had to be at least 18 years old, of either, have type 2 diabetes mellitus, be taking metformin monotherapy at a dose of at least ≥1500 mg/day for at least one month, have a HbA1c of 7.5-11% and fasting plasma glucose (FPG) ≥140 mg/dL. Those with type 1 diabetes mellitus, FPG > 270 mg/dL, HbA1c > 11%, severe cardiovascular diseases, Alanine transaminase/ Aspartate transaminase (ALT/AST) more than three times normal or direct bilirubin more than 1.3 times normal or kidney diseases (serum creatinine more than 1.5 mg/dL) were excluded.

In addition to their regular doses of metformin, 52 individuals were split into two groups and given either sitagliptin 100 mg (group 1) or pioglitazone 30 mg (group 2). According to already available literature and the likelihood of finishing it on time, the sample size was determined. Following up with the patients occurred at weeks 4, 12, and 16. The concurrent use of lipid-lowering medicines, antihypertensive drugs, and thyroid meds remained unchanged. The

change in HbA1c from week 0 to week 16 was the main efficacy end objective. Changes in body weight, lipid profile, and FPG were considered secondary end goals. During the course of the study, any unfavourable incidents in either group were also noted.

Statistical Analysis

Statistical analysis was done using computer software SPSS 16.0 version. *P* value of < 0.05 was considered significant. The data collected at 0 week were used as the baseline against which changes during therapy were compared. Change in HbA1c was calculated by ANCOVA model using various covariates. All statistical tests were two sided, and the results are presented as mean ± standard deviation.

Results

94 patients in total were examined between July 2021 and June 2022. 42 of them were eliminated because they did not meet the inclusion and exclusion criteria.

Two of the 52 study participants were lost to follow-up. Table 1 lists the demographic and biochemical characteristics of the individuals who were first enrolled.

At week zero, the baseline HbA1c levels for groups 1 and 2 were comparable. After 16 weeks of giving each study medication in combination with metformin, there was a significant drop in HbA1c in both groups. In group 1, the change in HbA1c from the beginning to the end was 0.656±0.21%, while in group 2, the change was 0.748± 0.35%. The two groups' respective modifications did not differ in a statistically meaningful way [Table 2]. In the study, 24% (n = 6) of the patients in group 1 and 2 (n = 7) of the patients in group 2 met the HbA1c 7% target. This distinction, nevertheless, was not statistically significant.

Table 1: Baseline demographic characters and biochemical parameters of the enrolled patients

Parameters	Group 1	Group 2	p-value
Age (years)	49.48±9.71	52.20±9.51	0.322
Sex [Male : Female]	15:10	14.11	1.00
Weight (kg)	72.1±13.8	72.68±10.76	0.86
Height (m)	1.57±0.076	1.59±0.086	0.46
BMI (kg/m^2)	29.035±4.966	28.707±3.729	0.79
Duration of diabetes (yrs.)	4.107±3.718	4.458±3.633	0.73
Duration of metformin (months)	13.92±11.28	14.46±13.56	
Dose of metformin (mg)	1865.38±354.44	1830±351.48	
Blood urea (mg%)	25.78±7.05	29.78±9.60	0.10
Serum creatinine (mg/dL)	0.870±0.25	0.909±0.22	0.55
Serum bilirubin (mg%)	0.532±0.21	0.516±0.17	0.76
Hemoglobin (gm/dL)	12.22±2.07	11.59±2.12	0.29
Fasting plasma glucose (mg/dL)	170.1±25.97	176.9±31.36	0.40
HbA_{1C} (%)	8.076±0.722	8.228±0.822	0.49
Total cholesterol (mg/dL)	193.2±43.46	204.12±42.39	0.37
LDL (mg/dL)	115±43	124±40	0.44
HDL (mg/dL)	176.16±78.49	195.92±56.16	0.38
Triglycerides (mg/dL)	42.52±5.52	41.04±5.69	0.35

At baseline, FPG was comparable across the two therapy groups. Both group 1 and group 2 showed a significant decrease in FPG at the conclusion of the 16-week study, with mean FPGs of 150.52±26.06 mg/dL (down from a baseline of 19.58 mg/dL) and 146.52±23.15 mg/dL (down from a baseline of 30.38 mg/dL), respectively. However, there was no discernible difference in the means of the FPG decreases between the two groups.

Table 2: Comparison of mean difference in pre and post treatment values of glycosylated hemoglobin in the two treatment groups

Group	Pre treatment Week 0 (mean±SD)	Post treatment Week 16 (mean±SD)	P-value within the groups	P-value between the groups
Treatment group 1 (n=25)	8.076±0.722	7.42±0.661	<0.0001	0.268
Treatment group 2 (n=25	8.228±0.822	7.48±0.662	<0.0001	t=1.12

After 16 weeks, treatment group 1 experienced a statistically significant mean weight loss of 0.58 kg from a baseline mean weight of 72.1±13.76 kg. In contrast, participants in group 2 experienced a statistically significant mean weight rise of 0.90 kg from a baseline of 72.68±10.83 kg.

At the conclusion of 16 weeks, the patients in group 1 reported a substantial drop in body mass index (BMI) from a mean BMI of 29.03±4.96 kg/m^2, but those in group 2 had a significant increase from a mean BMI of 28.71±3.73 kg/m^2. This variation between the groups was statistically significant as well.

During the course of the study, the mean blood TG levels in groups 1 and 2 significantly decreased to 10 mg/dL and 17.8 mg/dL, respectively. It was statistically significant that these two groups differed from one another. Both groups showed a considerable rise in HDL-C levels, which went from 42.52±5.51 mg/dL to 43.68±5.45 mg/dL in group 1 and from 41.04±5.69 mg/dL to 44.12±6.08 mg/dL in group 2, respectively.

Blood pressure, haemoglobin, total leukocyte count, liver function tests, and kidney function tests did not differ significantly from baseline between the two groups or within the group (P > 0.05) at the end of the study.

Both therapies in the current study were well tolerated and had no significant treatment-related side effects. One patient from group 1 in each of the following categories: headache, diarrhoea, and nausea. In group 2, two patients each described having a headache and edema.

Discussion

The patients in our study had a somewhat lower BMI, were a little bit younger in age, and had had diabetes for a little shorter time. This might be because, in contrast to other research that were multicentric and had a majority of Caucasian participants, the study population was totally urban Indian. Despite having a lower average BMI than the western population, Indians are more likely to develop diabetes at a younger age [7,8].

The average HbA1c reduction in the sitagliptin-treated group was 0.66 percent, which was close to the result of the earlier study published by Charbonnel *et al*. (0.65 percent HbA1c reduction in sitagliptin + metformin after 24 weeks). However, comparable studies by Hermansen *et al*., Scott *et al*., and Ludvik *et al*. found that the sitagliptin + metformin group experienced a

higher decrease in the HbA1c level, with reductions of 0.74% after 24 weeks, 0.73% after 18 weeks, and 1.13% after 24 weeks, respectively [9-12]. Before beginning combination therapy, Hermansen *et al*. used an anti-diabetic drug washout period that would have caused a considerable increase in HbA1c readings [10].

In a recent 18-week study, Reasner *et al*. found that the sitagliptin + metformin FDC group experienced a mean change from baseline HbA1c of 2.4%, compared to 1.8% decreases in the metformin monotherapy group [13]. The patients in the study had mean baseline HbA1c of 9.9%, whereas our study sample had mean baseline HbA1c of 8.076%. This difference in baseline HbA1c levels may be the cause of the larger HbA1c reduction.

In the pioglitazone-treated group of our study, the mean HbA1c reduction was 0.75%. The HbA1c level decreased more in the pioglitazone + metformin group, according to studies by Einhorn *et al*., Bolli *et al*., and Matthews *et al*.; the reductions were 1.36% after 72 weeks, 0.9% after 24 weeks, and 1% after 52 weeks, respectively [14-16]. This variation could be explained by the greater length of pharmacological treatment used in these investigations.

In our study, 24% of the sitagliptin-treated patients met the target of having a HbA1c level that was less than 7%. In a related 18-week research by Raz *et al*., 22% of patients with type 2 diabetes mellitus who received sitagliptin as an addition to metformin therapy achieved the target of <7% HbA1c [17]. But according to several other earlier studies, sitagliptin helped a higher percentage of patients reach their HbA1c goals (55% Scott *et al*., 63% Nauck *et al*.) [11-18].

The discrepancy between our study and Scott *et al*. can be attributed to the higher baseline mean HbA1c (Scott *et al*. 7.7% vs. 8.076% our study). Nauck *et al*. reported after 52 weeks, whereas we reported after 16 weeks, the percentage of patients achieving the target of <7% HbA1c level [18]

The decrease in FPG achieved with sitagliptin in this study (19.58 mg/dL after 16 weeks) was comparable to that seen by Hermansen *et al*. (20.1 mg/dL after 24 weeks) [10]. A larger decline in FPG (36.3 mg/dL after 24 weeks) was noted by Ludvik *et al* [12].

In comparison to the FPG reductions with pioglitazone seen by Bolli et al. (38 mg/dL after 24 weeks) and Matthews *et al*. (34.2 mg/dL after 52 weeks), which were observed in other studies, ours (30.38 mg/dL) was a little lower. According to Einhorn *et al*., the pioglitazone + metformin group experienced a higher decline in FPG (63 mg/dL at 72 weeks), which could be attributed to the longer research period [14-16].

In our study, the pioglitazone group exhibited a rise in the average body weight (0.9 kg after 16 weeks). This was less than what Bolli *et al*. and Umpierrez *et al*. found in earlier research (1.9 kg after 24 weeks), respectively (1.74 kg after 26 weeks) [15-19]. Greater adherence to dietary guidance and a shorter research period may be one factor.

However, after the first four weeks of treatment, weight declined in the sitagliptin group and subsequently stabilised at a level that was nearly identical to that of the pioglitazone group, while it decreased in the sitagliptin group. Sitagliptin appears to be largely weight neutral when combined with metformin, according to the results of other studies, with outcomes ranging from body weight reduction studied by Scott *et al*. (18 weeks, 0.4 kg), Nauck *et al*. (52 weeks, 1.5 kg), and Ludvik *et al*. to weight gain observed by Hermansen *et al*. (24 weeks + 0.8 kg) (24 weeks, 2.8 kg) [10-18]. Weight gain with diabetes therapy may increase insulin resistance and decrease adherence to the prescribed regimen. Therefore, the weight neutrality of DPP-4 inhibitors may provide a

significant therapeutic benefit in the control of diabetes [19].

Both sitagliptine and pioglitazone had an effect on each of the metrics for fasting lipid levels, increasing HDL-C and lowering triglyceride levels. However, the positive effects of pioglitazone on HDL-C and triglyceride levels were larger than those of sitagliptin (difference between groups, each $P < 0.05$).

There is a dearth of information in the literature about sitagliptine's impact on lipid profiles. Similar impacts on lipid profiles have been observed in studies by Tremblay and ourselves

Pioglitazone has been shown to have a positive effect on TG and HDL in a prior study [21,22] High triglyceride and low HDL cholesterol levels are strongly associated with cardiovascular morbidity and death in type 2 diabetic patients [22]. There have been worries about TZD liver damage [23]. Both sitagliptin and pioglitazone in our investigation resulted in a small, non-significant increase in the mean values of liver enzymes.

Nasopharyngitis, upper respiratory infections, and headaches are the most frequent side effects associated with DPP4 inhibitors that have been observed in clinical studys [24,25] Headache, diarrhoea, and nausea were the side effects of sitagliptin that were reported the most frequently in our study. Metformin may potentially be to blame for vomiting and diarrhoea since it is known to have gastrointestinal side effects [26]. The most frequent side effects noted in the pioglitazone group were edoema and weight gain, which have also been previously confirmed when pioglitazine was combined with metformin [15,16].

Conclusion

Sitagliptin is equally as effective and well tolerated when taken in combination with metformin as pioglitazone, but it has neither of these side effects. Sitagliptin may be a valuable addition to the current pharmacological toolbox for the management of individuals with type 2 diabetes mellitus due to its efficacy and favourable tolerability profile. Our findings addressing the noninferiority of DPP-4 inhibitors against TZDs as add-on therapy to metformin and their impact on treatment satisfaction or lipid profile warrant further research with larger sample sizes and longer follow-up periods.

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