

A pharmacoeconomic analysis to compare cost-effectiveness of metformin plus teneligliptin with metformin plus glimepiride in patients of type-2 diabetes mellitus

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ABSTRACT

Background: With the available evidence of early combined oral drug therapies being more effective in lowering blood glucose levels than maximal doses of a single drug, many clinicians are taking the aggressive approach of adding a sulfonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor to metformin as the initial therapy in type 2 diabetes mellitus (T2DM). Pharmacotherapy for a chronic disease like diabetes has substantial economic implications for patients especially in a developing country like India. So it is important to scientifically evaluate the cost-effectiveness of these commonly practiced combination therapies in the management of T2DM. **Materials and Methods:** This was a prospective observational randomized comparative study conducted over 8 weeks on patients of T2DM who were prescribed either of the two therapies of metformin (500 mg) plus glimepiride (1 mg) or metformin (500 mg) plus teneligliptin (20 mg). Cost-effectiveness analysis was done by calculating the expense incurred on 0.1% reduction in HbA1c and 1 mg/dl reduction in fasting plasma glucose (FPG)/post-prandial plasma glucose (PPG) levels after 8 weeks and compared for both the groups. The same was also evaluated for differences in BMI levels. **Results:** The cost-effectiveness for per unit reduction in HbA1c and FPG was significant in metformin plus glimepiride group as compared to the metformin plus teneligliptin group though it was comparable for both the groups for per unit PPG reduction. There was no significant change in BMI levels between the groups. **Conclusion:** Compared to metformin plus teneligliptin, metformin plus glimepiride is a significantly cost-effective therapy when used as an initial combination therapy in patients of T2DM in lowering HbA1c and FPG.

Keywords: Cost-effectiveness, glimepiride, teneligliptin

Introduction

Diabetes mellitus is a complex and heterogeneous group of chronic metabolic diseases characterized by hyperglycemia.^[1] Type 1 diabetes, caused by an immune-mediated destruction of insulin-producing pancreatic beta cells, is mainly diagnosed in the younger population. Type 2 diabetes mellitus (T2DM), which is more common in the elderly age group, is due to

insulin resistance along with progressive functional failure of the pancreatic beta cells.^[1] The prevalence of diabetes has been increasing explosively over the last few years. In 2015, there were 415 million people with diabetes all over the world and three quarters (75%) of these patients were living in low- and middle-income countries. The number has been predicted to rise to about 642 million by 2040 with alarming social, financial, and health system implications.^[2] India is poised to become the diabetic capital of the world with a patient population of

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69.2 million in 2015, which is projected to increase to 123.5 million in 2040.^[3]

Proper glycemic control, which decreases the development and progression of diabetes-related complications, is difficult to be achieved in nearly half of the patients with T2DM.^[4] With the available evidence of early combined oral drug therapies being more effective in lowering blood glucose levels than maximal doses of a single drug, many clinicians are taking the aggressive approach of adding a sulfonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor to metformin as the initial therapy.^[5] Sulfonylureas have been the first choice to be used as add-on therapy to metformin in Indian clinical settings, ever since their introduction.^[6] Among the sulfonylureas, glimepiride, a second generation sulfonylurea, is commonly prescribed, due to its relatively better efficacy and safety profile. Teneligliptin, a relatively newer DPP-4 inhibitor, is also being used in combination with metformin in the management of T2DM.^[7]

Pharmacotherapy for a chronic disease like diabetes has substantial economic implications for patients especially in a developing country like India. Only efficacy may not justify a drug choice for long term therapy as the cost factor is equally important. Similarly, an apparently costlier drug or therapeutic regimen may also turn out to be a good choice when seen in the context of efficacy and tolerability. So, it is important to scientifically evaluate the cost-effectiveness of these two commonly practiced combination therapies in the management of T2DM.

There have been a few studies in other countries to compare the cost-effectiveness of similar combination therapies in T2DM, but to the best of our knowledge, such study has not yet been done in Indian patients. So, the current study was done to evaluate the relative cost-effectiveness of these two combination therapies in the management of T2DM patients in our population. The objectives of the study were (a) to evaluate the cost-effectiveness of combination therapy of metformin plus glimepiride as compared to metformin plus teneligliptin in patients of T2DM and (b) to evaluate and compare the safety and tolerability of both the above combination therapies in patients of T2DM.

Materials and Methods

This was a prospective observational randomized comparative study conducted over eight weeks by Department of Pharmacology in collaboration with the Department of Medicine. Prior approval of the study protocol was taken from the Institutional Ethics Committee (vide Ref. No. SU/SMS and R/76-A/2018/93) and only those patients volunteering to participate and provide written informed consent were included in the study. Participants were recruited as outpatients in the Medicine Department. Patients with any significant renal/cardiovascular/hepatic disease or with any history of such disease in recent past (within 6 months) were excluded from the study.

Study design

Newly diagnosed patients of T2DM of either sex with HbA1c more than 6.5% and FPG of more than 126 mg/dl, judged to require initial combination therapy, were prescribed either of the two therapies of metformin (500 mg) plus glimepiride (1 mg) or metformin (500 mg) plus teneligliptin (20 mg) based on randomization. A total of thirty-nine patients completed the study after providing written informed consent and fulfilling the inclusion and exclusion criteria for the study. Twenty patients were on metformin (500 mg) plus glimepiride (1 mg) whereas 19 patients were in the other group on metformin (500 mg) plus teneligliptin (20 mg). Baseline demographic characteristics of the patients were recorded for both the groups. HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and body mass index (BMI) for each patient in both the groups were recorded on initial visit and after 8 weeks of therapy. Measurement of HbA1c, FPG, and PPG was performed at the central laboratory of the hospital.

Therapeutic efficacy

The efficacy of the two drug combinations was assessed by HbA1C, FPG, and PPG reductions at 8 weeks from the baseline values. HbA1C is usually evaluated after 8–12 weeks and changes in HbA1C after 8 weeks have also been used as a measure of efficacy in previous studies.^[8] Change in BMI score was also noted and evaluated.

Cost-effectiveness analysis (CEA)

CEA was conducted by using the cost and effectiveness data for both the drug combinations. The cost data comprised of the direct costs involved in buying the drugs as well as any other expense on management of the adverse events during the course of the treatment for the respective regimen. As the investigations were similar in both the arms the cost for the investigations was not included in the data. The cost of each treatment group was calculated by multiplying the daily unit cost by the number of treatment days (for 2 months) in the two arms. CEA was derived by calculating the expense incurred on 0.1% reduction in HbA1c and 1 mg/dl reduction in FPG after 8 weeks and compared for both the groups. The same was also to be evaluated for the differences in BMI levels, if any.

If a combination therapy was more efficacious as well as costlier than the other, then incremental cost-effectiveness ratio (ICER) was to be applied to assess the extra cost per unit of outcome incurred. ICER is calculated as: $ICER = (\text{Cost of combination therapy in costlier therapy group for the two months} - \text{Cost of combination therapy in the other group}) / (\text{Effectiveness in the costlier group} - \text{Effectiveness in the other group})$.^[9]

Safety and tolerability

Treatment-emergent adverse events during the study period were to be recorded and evaluated for their possible relationship to the medications. All such events for both the groups were to be assessed to compare the safety and tolerability of both the combination therapies.

Statistics

Evaluation of the data was done by applying the paired and unpaired t-tests. $P < 0.05$ was considered significant for the study.

Results

Baseline characteristics in both the groups were comparable [Table 1] and there was no significant difference in the mean age, HbA1c, FPG, PPG, and BMI levels in both the groups.

The glycemic parameters (HbA1c %, FPG, and PPG) after therapy improved very significantly in both the treatment arms as compared to the levels before treatment [Tables 2 and 3]. But no significant changes were there in the mean BMI levels before and after therapy in any of the treatment groups.

Both the groups were found to be comparable in efficacy in reducing mean HbA1c%, FPG, and PPG without any significant difference [Table 4]. There was no significant change in BMI levels in one group as compared to the other.

The cost effectiveness analysis showed that mean cost (in rupees) of per unit reduction in HbA1c and FPG in metformin plus glimepiride group was significantly less than in the metformin plus teneligliptin. The cost-effectiveness for per unit reduction in FPG was highly significant in metformin plus glimepiride group though it was comparable for both the groups for per unit PPG reduction [Table 5].

Both the groups of drugs were well tolerated by the patients without any major adverse effect requiring management during the study period.

Discussion

There is a need to understand the relative cost-effectiveness of the prescribed drugs for a chronic disease like diabetes in planning to achieve the desired therapeutic goals more effectively without being a financial burden to the patient. A comparative evaluation based on scientific analysis rather than the apparent cost of the therapy helps the decision-makers choose a more cost-effective treatment option, especially for patients in the socioeconomic backdrop of a developing country like India. Primary health care physicians deal with patients from varied strata and in a country like India a large part of their patient population belongs to poor socioeconomic background. Hence, cost-effectiveness becomes an even more important deciding factor in clinical practice.

Diabetes is associated with significantly higher lifetime medical expenditures while resulting in reduced life expectancy with substantial burden on the society.^[10] Combination therapies are commonly being used by many physicians now, who believe in aggressive control of the blood sugar. Though the standard treatment guidelines in diabetes mellitus still advocate the

Table 1: Group wise baseline patient characteristics

Baseline Parameters	Metformin plus glimepiride	Metformin plus teneligliptin	P value
Age (mean±sd) years	47.64±12.45	48.75±13.20	0.403*
HbA1c (mean±sd) %	8.58±1.48	9.06±1.19	0.212*
FPG (mean±sd) mg/dl	172.28±31.52	160.5±25.45	0.118*
PPG (mean±sd) mg/dl	271.21±50.18	256.75±34.52	0.162*
BMI (mean±sd) kg/m ²	25.70±2.01	24.17±2.69	0.062*

HbA1c: Hemoglobin A1c; PPG: Post-prandial plasma glucose; FPG: Fasting plasma glucose; BMI: Body mass Index *Not significant

Table 2: Parameters before and after therapy (at 8 weeks) for Group 1

Metformin plus glimepiride	Baseline	After 8 weeks	P value
HbA1c %	8.581±1.48	6.96±1.57	0.00164***
FPG (mg/dl)	172.28±31.52	136.5±26.10	0.00006***
PPG (mg/dl)	271.21±50.18	201.51±40.23	0.00096***
BMI (kg/m ²)	25.70±2.01	25.56±2.15	0.0884*

HbA1c: Hemoglobin A1c; PPG: Post-prandial plasma glucose; FPG: Fasting plasma glucose; BMI: Body mass Index *Not significant ***Highly significant

Table 3: Parameters before and after therapy (at 8 weeks) Group 2

Metformin plus teneligliptin	Baseline	After 8 weeks	P value
HbA1c %	9.06±1.19	7.71±1.18	0.0025***
FPG (mg/dl)	160.5±25.45	127.55±22.27	0.00078***
PPG (mg/dl)	256.75±34.52	192.61±40.71	0.00022***
BMI (kg/m ²)	24.17±2.69	24.04±2.87	0.2378*

HbA1c: Hemoglobin A1c; PPG: Post-prandial plasma glucose; FPG: Fasting plasma glucose; BMI: Body mass Index *Not significant ***Highly significant

Table 4: Parameters compared between the two groups at 8 weeks follow up

Parameters	Metformin plus glimepiride	Metformin plus teneligliptin	P value
Reduction in HbA1c %	1.7±0.68	1.52±0.71	0.342*
Reduction in FPG (mg/dl)	35.78±23.89	32.95±29.4	0.382*
Reduction in PPG (mg/dl)	69.7±47.12	64.14±51.35	0.375*
Change in BMI (kg/m ²)	0.14±0.24	0.12±0.44	0.881*

HbA1c: Hemoglobin A1c; PPG: Post-prandial plasma glucose; FPG: Fasting plasma glucose; BMI: Body mass Index *Not significant

Table 5: Cost-effectiveness of both groups at 8 weeks

Cost of Reducing per unit parameter (in rupees)	Metformin plus glimepiride	Metformin plus teneligliptin	P value
HbA1c by 0.1%	12.77±3.80	19.78±6.51	0.031**
FPG by 1 mg/dl	7.45±3.95	19.13±13.96	0.002***
PPG by 1 mg/dl	6.40±7.45	8.72±5.62	0.244*

HbA1c: Hemoglobin A1c; PPG: Post-prandial plasma glucose; FPG: Fasting plasma glucose; BMI: Body mass Index *Not significant ***Highly significant **Significant

addition of a second drug after initial trial of monotherapy, the practice of prescribing combination therapies as initial therapies has been advocated in many studies and has become an increasingly common practice.^[11]

Some earlier studies have been conducted in Caucasian population comparing the efficacy of DPP-4 inhibitors or sulfonylureas as add-on therapies. One study compared the short-term cost-effectiveness of liraglutide versus sitagliptin in patients with type 2 diabetes failing metformin monotherapy.^[12] Another study evaluated the cost-effectiveness of saxagliptin in type 2 diabetes mellitus in American patients.^[13] A recent study found the treatment pathway with DPP-4 inhibitors as the cost-effective second-line therapy compared to sulfonylureas from the US health care payer perspective.^[14] There had been no direct comparison for cost-effectiveness of teneligliptin with sulfonylureas as combination therapy with metformin in Indian T2DM patients. So, this study was undertaken to evaluate the relative cost-effectiveness of these two combination therapies.

In this study both the groups were efficacious in reducing the glycemic parameters as expected, because both the drug combinations are approved and established drugs in the management of DM. When compared to each other the groups were comparable in modulating the glycemic parameters in this study without any significant difference in efficacy. An earlier systemic review and meta-analysis had shown the glimepiride/metformin to be more effective despite slight differences in adverse effects.^[15] The meta-analysis had concluded that the glimepiride/metformin combination, both due to cost as well as effectiveness and safety, might be the preferential treatment for most T2DM patients. In the present study, however, the long-term superiority in efficacy was not evaluated and both the groups had comparable initial efficacy.

None of the therapies produced significant change in mean BMI in the present study. Glimepiride has been shown to produce weight gain and gliptins to cause some weight loss after long-term therapy.^[10,16] The present study was of shorter duration and both the groups had comparable short term effects on BMI which were not significant.

When both the groups were compared for cost-effectiveness, metformin plus glimepiride was significantly more cost-effective as compared to metformin plus teneligliptin in reducing the glycemic parameters though the cost-effectiveness for PPG reduction was similar for both the groups. Due to their predominant action on food related glucose increase gliptins have been shown to be efficacious in especially reducing PPG.^[17] But overall, the gliptins were less cost effective as compared to glimepiride when used with metformin in reducing the glycemic parameters in the present study.

The study emphasizes the need to evaluate the cost-effectiveness of treatment regimens as the primary care physicians dealing with economically backward patients need to know whether a particular regimen is also cost-effective rather than just being an effective alternative. Sometimes a costly therapy is justified when judged in the context of superior efficacy or better tolerability, so scientific evaluations in the context of a prevalent disease like

diabetes would highlight the comparative merits of the regimens to the primary care physicians for their patients.

As both the combination therapies were comparable in efficacy, the incremental cost-effectiveness ratio (ICER) could not be applied in the current study. The small sample size and short-term evaluation in terms of cost-effectiveness with mainly glycemic indices as parameter are limitations of this study. The long-term adverse effects, costs incurred in treating such adverse effects and long-term advantages of these combination therapies with respect to life expectancy and quality adjusted life years on larger population need to be further evaluated in the Indian patients for in depth pharmacoeconomic comparison.

Conclusion

Compared to metformin plus teneligliptin, metformin plus glimepiride is a significantly cost-effective therapy when used as an initial combination therapy in patients of T2DM in lowering HbA1c and FBS, though cost-effectiveness for reducing PPBS was similar for both.

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Conflicts of interest

There are no conflicts of interest.

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