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COMPARING EFFICACY OF TRELAGLIPTIN VERUS SITAGLIPTIN IN PATIENTS WITH INADEQUATELY CONTROLLED TYPE II DIABETES ON METFORMIN ALONE

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Abstract

Objective: *The purpose of the research is the comparison of efficacy of trelagliptin versus sitagliptin in patients with inadequately controlled type II diabetes on metformin alone*

Study Design: *Randomized Control Trial*

Study Duration: *06 months from Oct 2024-March 2025*

Study Place: *Department of Medicine, CMH Lahore*

Methods: *A randomized, parallel, open-label, prospective study was conducted to compare the efficacy and safety of once-weekly trelagliptin versus once-daily sitagliptin in type II diabetes patients inadequately controlled on metformin. A total of 120 participants were randomized equally into two groups. Primary outcome was change in HbA1c after 12 weeks; secondary outcomes included FPG, PPG, body weight, and adverse events. Data were analyzed using SPSS v26, with $p<0.05$ as significant.*

Results: *In this 12-week study of 120 patients with type II diabetes, both trelagliptin and sitagliptin significantly improved HbA1c and glucose levels. Trelagliptin showed a slightly greater HbA1c reduction (-1.21% vs. -1.08%, $p=0.048$) and higher achievement of HbA1c <7% (61.7% vs. 50%, $p=0.042$). Both drugs were weight-neutral, well tolerated, and caused only mild gastrointestinal side effects, with no severe hypoglycemia or organ dysfunction observed*

Conclusion: *Both trelagliptin and sitagliptin had significant beneficial glycemic control when added to metformin in patients with inadequately controlled type II diabetes. Their safety and tolerance profiles were similar. Sitagliptin has long-term evidence and cardiovascular safety, whereas trelagliptin's once weekly dosing may enhance patient adherence.*

INTRODUCTION

Type II diabetes mellitus (T2DM) is a chronic and progressive metabolic disorder with insulin resistance, impaired insulin secretion and hepatic glucose production, leading to persistent hyperglycemia (1). Globally, the prevalence of T2DM has increased to epidemic proportions with an estimated 537 million adults with the condition in 2021, a figure expected to increase to 643 million by 2030 (2). The burden is particularly high in the developing countries, including Pakistan, due to urbanization, sedentary lifestyles and unhealthy dietary patterns (3). Uncontrolled diabetes is a major contributor to morbidity and mortality from the microvascular and macrovascular complications like nephropathy, neuropathy, retinopathy, cardiovascular disease, and stroke (4). These complications not only affect quality of life but also take a heavy toll on healthcare systems around the world.

The management of T2DM mainly revolves around achieving and maintaining optimal glycemic control using a combination of lifestyle modification with pharmacotherapy. The first line pharmacological agent, metformin, which belongs to the biguanide class, is based on efficacy, safety, cost-effectiveness, and cardiovascular benefit (5). It works primarily by reducing the production of glucose in the liver and enhancing the sensitivity of body cells (peripheral tissue) to insulin. However, despite its widespread use, around 40-50% of patients do not achieve glycemic targets with metformin monotherapy and a second agent needs to be added (6).

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a group of oral antihyperglycemic agents that have increased in prominence as an add-on medication to metformin. These agents increase the duration of action of incretin hormones i.e., glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that promote insulin secretion and inhibit glucagon release in a glucose-dependent fashion.8 The first approved DPP-4 inhibitor Sitagliptin has been shown to be effective in reducing glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG), in combination with metformin, without significant hypoglycemia or weight gain (7).

Trelagliptin, a novel once-weekly DPP-4 inhibitor, has the benefit of patient compliance advantage owing to its long dosing interval. Clinical studies have found that trelagliptin offers similar efficacy and safety as daily DPP-4 inhibitors such as sitagliptin that sustained DPP-4 inhibition and stable glycemic control. Because of its pharmacokinetic profile, it is possible to achieve stable plasma concentrations, which may be more conducive to adherence and long-term glycemic control. However, comparative data on efficacy of trelagliptin versus sitagliptin in patients who are not adequately controlled on metformin alone are still limited (8,9).

Therefore the purpose of this study is to compare the efficacy and safety of trelagliptin and sitagliptin as add-on-therapy to metformin in patients with inadequate controlled type II diabetes. By assessing outcomes such as changes in HbA1c, fasting blood glucose and postprandial glucose blood changes, and adverse event profiles, this research aims to assess whether the once weekly dosing of trelagliptin provides similar or better glycemic control. The results will help in the optimization of combination therapy regimens, and/or improve adherence by patients with T2DM.

Methodology:

It was a randomized, parallel, prospective, open comparison study, conducted in the Department of Medicine, CMH Lahore, a six-month period from Oct 24 to Dec 25. The aim of the study was to evaluate the effectiveness and safety of single (one weekly) dose of trelagliptin and single (one daily) dose of sitagliptin in patients with type II diabetes mellitus (T2DM) who were poorly managed on metformin monotherapy. Prior to the start, ethical approval was received by the Institutional Review Board (IRB) and all of the participants signed written informed consent as per the Declaration of Helsinki. The sample size was determined using the hypothesis that a difference of 0.5 per cent in glycated hemoglobin (HbA1c) between the two treatment groups was a clinically significant difference. Taking into consideration a standard deviation of 1.0, a power of 80, and alpha level of 0.05, a minimum of 50 patients in each group was needed. The number of participants was determined as 120 participants

(60 patients per group) to consider a 20 percent dropout rate.

Inclusion Criteria

The participants could be included based on the following criteria:

1. Adults aged between 30 and 65 years of age with T2DM based on American Diabetes Association (ADA) criteria.
2. On metformin monotherapy (≥1500 mg/day) of at least 12 weeks before screening.
3. A metformin-treated HbA1c of 7.0 -9.5%.
4. FPG of less than 250mg/dL at the baseline.
5. Premise to abide by the study procedures and follow-up visits.

Exclusion Criteria

The exclusion criteria were:

1. Type 1 diabetes mellitus or secondary diabetes.
2. Insulin or other oral antidiabetic drugs use in the last 3 months.
3. Considerable hepatic (ALT / AST > 2.5x ULN) or renal dysfunction (eGFR <60 mL/min/1.73 m 2).
4. Pancreatitis, heart failure, or hypersensitivity to DPP-4 inhibitors.
5. Women who are pregnant, lactating or women who intends to conceive within the study period.

The eligibility criteria were randomly assigned to two groups of eligibility participants in a 1:1 ratio, with the help of a computer-generated randomization list:

- Group A (Trelagliptin group): Trelagliptin 100 mg once a week was added to the current metformin treatment.
- Group B (Sitagliptin group): The sample took Sitagliptin 100 mg per day with metformin.

The entire sample used their metformin starting dose during the study. Diet and exercise advice were also strengthened as the lifestyle modification counseling at every visit.

Each of the participants was examined by medical history and physical examination and laboratory analysis at the baseline. The follow-up assessments were 4, 8, and 12 weeks. The parameters measured at every visit were the fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA1c, body weight, and blood pressure. The level of HbA1c was determined using high-performance liquid chromatography (HPLC) both at baseline and 12 weeks. Enzymatic colorimetric measurements of FPG and PPG were done after an overnight fast.

The main performance measure was the change of HbA1c (%) between baseline and 12 weeks.

The secondary endpoints were:

- Alterations of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG).
- Percentage of patients with HbA1c that is less than 7.0.
- Change in body weight and body mass index (BMI).
- Incidences of adverse events, such as gastrointestinal disturbances and hypoglycemia.

The assessment of safety was conducted with the help of the observation of adverse events, physical examination, vital signs, and laboratory research (liver and renal function tests) at the beginning and the end of the study.

The SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Continuous variables were expressed in terms of mean standard deviation (SD), and categorical variables were expressed in terms of frequencies and percentage. The t-test was employed to compare the continuous variables between groups using the Student and Chi-square was used to compare the categorical variables. Paired t-tests were applied to assess changes between baseline in each group. A p-value lower than 0.05 was taken as statistically significant.

Results:

A total of 120 patients with inadequately controlled type II diabetes mellitus were included and randomly allocated equally to two groups (60 in the Trelagliptin group and 60 in the Sitagliptin group). Baseline demographic and clinical characteristics of the two groups were similar (Table 1).

The mean age of the subjects was 52.3 +- 8.4 years among the Trelagliptin group and 51.6 +- 7.9 years among the Sitagliptin group. The two groups were similar in age, sex, and race, however there was a slight predominance of males (55% vs. 53%). Mean

duration of diabetes was 6.2 + 2.7 years in Trelagliptin group and 6.4 + 2.5 years in Sitagliptin group. Baseline HbA1c was 8.41 +- 0.67% and 8.39 +- 0.62%, respectively and there was no statistically significant difference (p=0.81).

At the end of 12 weeks, both treatment groups had significant improvements in glycemic parameters when compared to baseline (p<0.001 within groups). However, the difference in reduction of HbA1c was higher in the Trelagliptin group than in the Sitagliptin group.

The mean change in HbA1c was -1.21 +- 0.42% in the Trelagliptin group and -1.08 +- 0.45% in the Sitagliptin group (p=0.048). Similarly, fasting plasma glucose (FPG) was decreased by -38.4 +- 15.3 and -32.7 +- 14.9 mg/dL, respectively in the Trelagliptin and Sitagliptin groups (p=0.036). Postprandial plasma glucose (PPG) was reduced by -58.3 +- 20.7 mg/dL and -51.1+ -21.2 mg/dL respectively (p=0.044). (chart 1,2)

At week 12, 61.7% of patients in the Trelagliptin group reached HbA1c <7.0% compared with 50.0% in Sitagliptin group (p=0.042). This indicates a small but considerable benefit of trelagliptin in the achievement of target glycemic control. (chart 3)

Both groups showed small but non-significant decreases in body weight and BMI. Mean body weight had a reduction of 0.7 +- 1.2 kg in the Trelagliptin group and 0.5 +- 1.0 kg in the Sitagliptin group (p=0.39). This is near to the weight-neutral profile of DPP-4 inhibitors and no significant difference between the intergroup was found.

Both drugs were well tolerated. Mild GI distress was experienced in 6.7% in the Trelagliptin group and 8.3% in the Sitagliptin group (p = 0.67). No severe hypoglycemia, pancreatitis, or hepatic dysfunction was observed in both groups. Labs for liver and renal functions were normal during the study period. (table 4)

Parameter	Trelagliptin n=60	Sitagliptin n=60	p-value
Age	52.3 ± 8.4	51.6 ± 7.9	.68
Gender M/F	33/27	32/28	.85
Diabetes Duration	6.2 ± 2.7	6.4 ± 2.5	.71
BMI	27.4 ± 3.5	27.6 ± 3.1	.77
HBA1C	8.41 ± 0.67	8.39 ± 0.62	.81
Fasting Sugar (mg/dl)	172.6 ± 24.5	173.8 ± 23.9	.84
Post prandial Sugar (mg/dl)	244.7 ± 28.6	246.9 ± 29.1	.68

Table 1. Baseline demographic and clinical characteristics

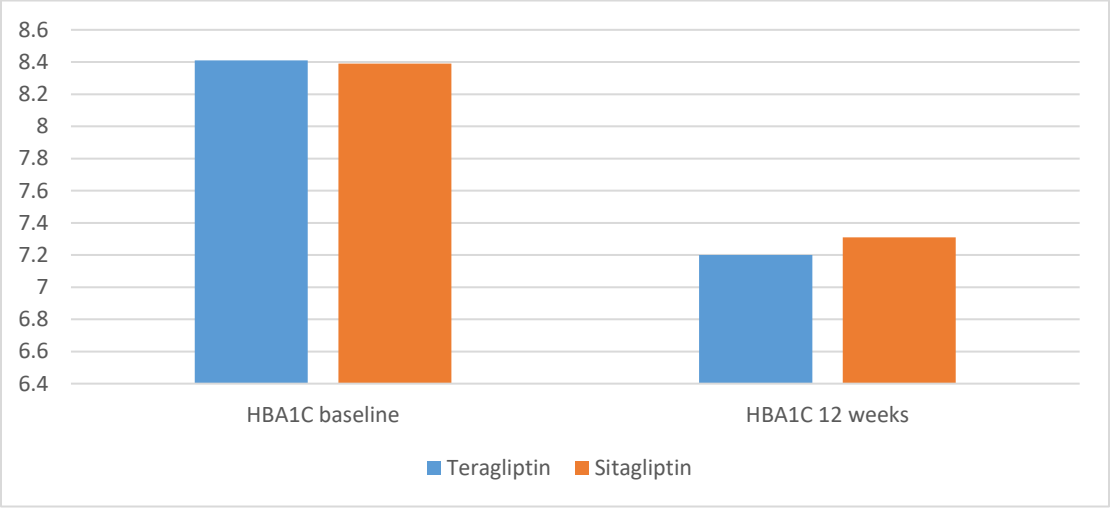

Chart 1: Comparison of efficacy of Trelagliptin and Sitagliptin after 12 weeks

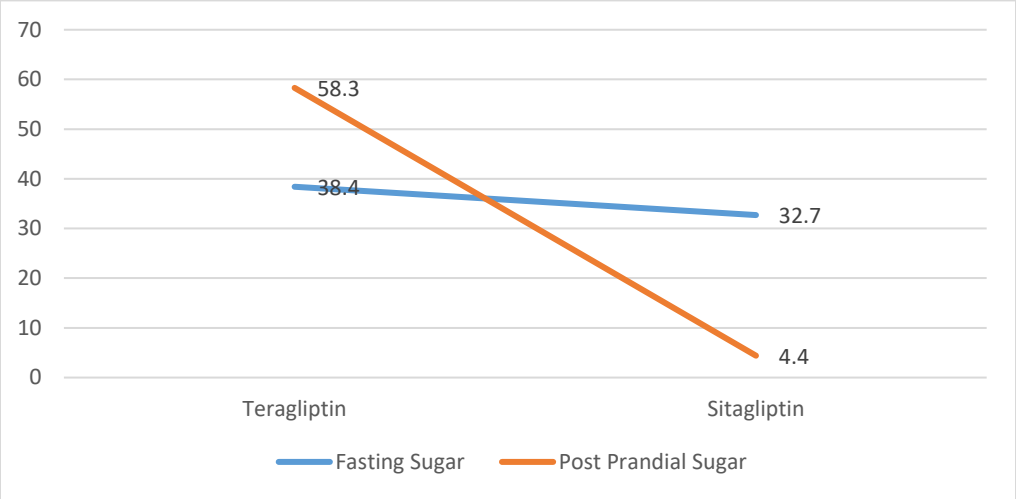

Chart 2: Comparison of sugars levels between two drug groups

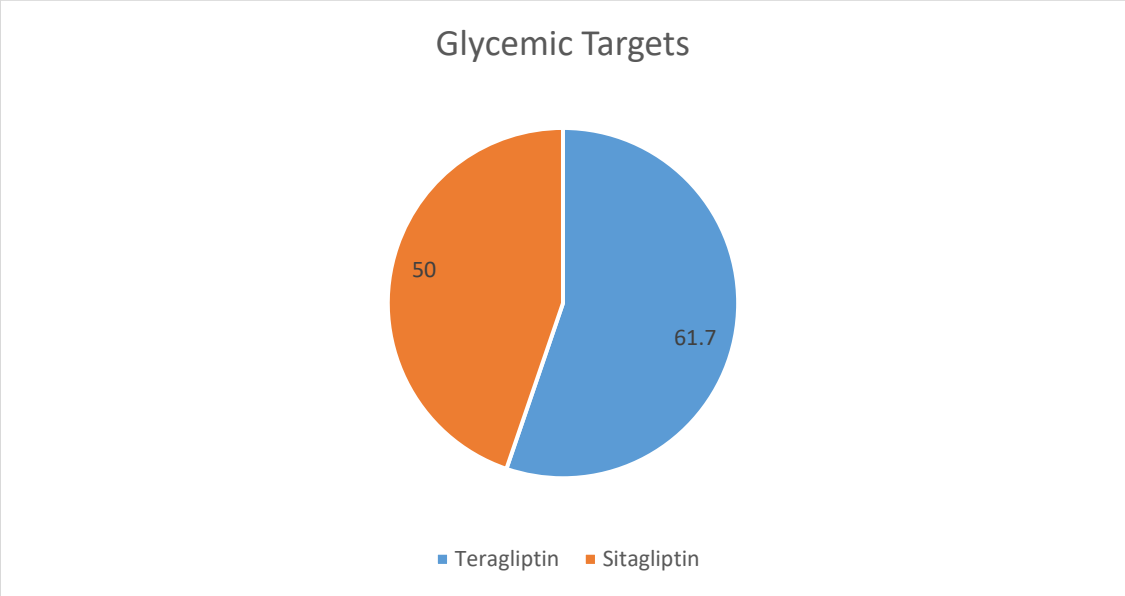

Chart 3: Glycemic Target comparison between two groups

Parameter	Trelagliptin	Sitagliptin
Hypoglycemia	0	0
GI Disturbance	4	5
Headache	2	3
Deranged LFT	0	1

Table 4: Side effect profile of 2 drug group

Discussion:

In this study, the effectiveness and safety of once weekly trelagliptin compared to once daily sitagliptin as add-on treatment to metformin in patients with poorly controlled type II diabetes mellitus (T2DM) was compared. Both drugs had a significant effect on enhancing glycemic parameters such as glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) after 12 weeks of therapy. However, trelagliptin showed slightly greater decreases in HbA1c, FPG and PPG values, as well as a higher number of patients achieving HbA1c <=7.0%, suggesting greater efficacy and similar safety to sitagliptin.(10)

The mean change in HbA1c with trelagliptin (-1.21%) and sitagliptin (-1.08%) in our study is in line with trials reported previously for DPP-4 inhibitors as add-on therapy to metformin. Charbonnel et al. (11) showed mean HbA1c improvement of 0.65% with sitagliptin 100 mg once a day after 24 weeks and

similar efficacy was also observed when sitagliptin was used with metformin according to Aschner et al. (12). These results confirm the efficacy of sitagliptin in metformin monotherapy inadequately controlled patients. Trelagliptin was, however, slightly more effective than vildagliptin in our cohort in terms of HbA1c reduction, which is similar to the results of a randomised controlled trial by Terauchi et al. (13), in which once weekly trelagliptin 100 mg was shown to have similar or better glycaemic control than daily DPP-4 inhibitors after 12 weeks.

The better effect of trelagliptin might be due to the pharmacokinetic properties such as a longer half-life and an almost 90% DPP-4 inhibition over the duration of the dosing interval (14). This leads to continued incretin action for extended periods of time and thereby to more stable glycemic control and greater patient compliance due to fewer doses. Better compliance using once weekly medications has been described for chronic diseases including diabetes, where pill burden is a major determinant of treatment success (15).

In the present study, the target HbA1c (<7.0%) was reached in 61.7% of patients with trelagliptin and 50.0% with sitagliptin, with a statistically significant difference between the 2 groups (p=0.042). This finding is in line with those of Yang et al. (16), who found that trelagliptin met HbA1c targets in a larger proportion of patients than sitagliptin in Chinese populations. The reproducibility of these results in ethnic subgroups confirms that trelagliptin is an effective and potent once-daily glucagon-like peptide 4 (DPP-4) inhibitor.

Our study found a clinically significant improvement in the fasting and postprandial glucose levels with trelagliptin (-38.4 mg/dL and -58.3 mg/dL, respectively), which also provides additional evidence of its strong glucose-lowering effect. Similar results were reported by Kadowaki et al. (17), who showed that trelagliptin caused a significant decrease in FPG and PPG levels in patients with T2DM after 12 weeks of therapy. Other studies have produced similar results proving the consistency of both agents in improving fasting and postprandial glycemia.

Both treatment groups had small changes in body weight and BMI that were consistent with the weight-neutral profile of DPP-4 inhibitors (18). This property provides a clear advantage over insulin secretagogues and thiazolidinediones, which are frequently accompanied by a gain in weight. The lack of significant weight gain has a positive effect on long-term patient compliance and the management of cardiovascular risk.

Safety analysis showed that both drugs were well tolerated without any major adverse events or hypoglycemic episodes. Mild gastrointestinal discomfort and headache were the only most frequently reported side effects, but these were temporary and did not necessitate discontinuation of treatment. These results agree with previous reports with DPP-4 inhibitors, which consistently exhibit excellent safety profiles, low hypo-glycemia risk and low hepatic or renal toxicity (19).

The demonstration of an equally good or even slightly better efficacy for trelagliptin, which is administered once a week, is an important feature of this study. This is consistent with emerging evidence that adherence in patients is greatly enhanced when simplified dosing regimens are used (20). "Considering that noncompliance with antidiabetic therapy continues to be the biggest obstacle to glycemic goal achievement, trelagliptin may be a very useful option, especially in patients who have difficulty with complex multidrug therapy regimens.

The clinical implications of these results are that trelagliptin may be able to provide equivalent glycemic control with fewer doses with comparable safety. This holds especially true in resource constrained settings like Pakistan where adherence to daily therapy can be difficult as a result of socioeconomic constraints and problems with access to healthcare (21). In addition, availability of affordable once weekly DPP-4 inhibitors has the potential to improve treatment satisfaction and long-term outcomes.

However, this study has a few limitations. The relatively short duration (12 weeks) may not adequately represent long-term glycemic control or cardiovascular safety outcomes. Moreover, the open-label design is potentially prone to bias, but, while randomization reduced the selection effects, it was not used. Larger multicenter, double-blind trials with longer follow-up-period are recommended to validate these results, as well as to investigate durability of response, safety of treatment in a diverse population of patients, and cost-effectiveness.

In conclusion, the present study has shown that both trelagliptin and sitagliptin, when added to metformin, have a significant synergistic effect on glycemic control in patients with inadequately controlled type II diabetes mellitus. With a once weekly administration, trelagliptin is slightly more effective in reducing HbA1c, FPG and PPG with an excellent safety profile. Its simplified regimen and similar efficacy make it a promising therapeutic substitute for enhancing adherence and optimising diabetes management.

Several international randomised trials and pooled analyses have demonstrated that DPP-4 inhibitors lower HbA1c by ~0.5-1.2% with the addition of metformin, have a low risk of hypoglycemia and are weight neutral. Sitagliptin's efficacy as an adjunct to metformin was determined from initial large multicenter trials and long-term studies, which showed clinically significant HbA1c reductions (usually 0.6-0.9% over 12-24 weeks) and excellent tolerability in diverse ethnic groups1,2,3. These sitagliptin trials provided a gold standard that has guided subsequent head to head and class comparisons.

Trelagliptin (once weekly dosing) was developed to enhance adherence while providing for constant inhibition of DPP-4. Phase II/III studies in Japan, China, India and other areas showed that once-weekly trelagliptin 100 mg provided HbA1c reductions similar to the daily DPP-4 inhibitor and to active comparators, such as vildagliptin, during 12-16 week studies with an acceptable safety profile and no new safety signals (18). Key Japanese and multinational studies showed sustained DPP-4 suppression throughout the dosing interval, which offers a pharmacologic basis for similar efficacy with less frequent dosing (19).

Although evidence is still scarce, it is increasing. Most recent randomized comparisons (or non-inferiority trials) of once-weekly trelagliptin compared with daily DPP-4 inhibitors (sitagliptin or vildagliptin) have shown non-inferiority in relation to glycemic endpoints with some studies reporting numeric benefits for trelagliptin for mean HbA1c reduction or target achievement, differences commonly small and of borderline significance (18). Where differences favour trelagliptin, authors have mostly cited steady DPP-4 inhibition and possible benefits on adherence when compared to the once-daily dose of the DPP-4 inhibitor, rather than huge pharmacodynamic differences.

The safety profile of all international studies is similar: a low incidence of hypoglycemia, little number of serious adverse events related to the drug, and rare alteration of liver or pancreatic enzymes. Sitagliptin (most extensively studied worldwide) and trelagliptin (mostly studied in East Asian and South Asian populations with emerging data from other parts of the world) are similar with respect to tolerability in trials up to 26 weeks, but only sitagliptin has long-term data for cardiovascular and pancreatic safety due to earlier and more global use (20)

Important variation between studies should be noted. Populations differ: most trelagliptin trials were carried out in Japanese or Chinese populations with lower baseline body-mass index and different background therapies compared with that in the Western populations, which may affect absolute changes in HbA1c as well as safety signals. Trial durations are also variable, with most of the head-to-head trials of trelagliptin being relatively short (12 to 24 weeks), which limits the conclusions that can be drawn about durability of effect, long-term safety,

and cardiovascular outcomes, where there are larger data sets for sitagliptin (including cardiovascular safety trials and real-world studies. (22)

Meta-analyses and recent systematic reviews of DPP-4 inhibitors conclude that class effects (modest HbA1c lowering, weight neutrality, low hypoglycemia) are consistent across agents but note that there are gaps in the literature: direct, large, long-duration, multicenter comparisons between once-weekly and daily DPP-4 inhibitors are sparse; studies comparing head-to-head agents in different ethnicities and healthcare settings are needed; and cost-effectiveness and adherence advantages of weekly dosing need to be confirmed in real-world settings.

In conclusion, the results of international studies corroborate that trelagliptin is as effective and safe as sitagliptin in glycemic efficacy in addition to metformin, with the major potential advantage of once-weekly administration that may improve compliance. Lack of data about longer-term outcomes and generalizability, and health-economic outcomes to larger populations are areas of ongoing uncertainty which will need to be resolved in larger, longer, and more geographically diverse trials.

Limitation of Study:

The study has been conducted on limited number of people and is single center. Hence its results cannot be generalized on population level. To get better results, a large and multi center trial and with comparison of more drugs group should be carried out.

Conclusion:

The comparative evaluation of trelagliptin and sitagliptin as add-on therapies to metformin in patients who have inadequately controlled type II diabetes mellitus shows that both agents are effective in improving glycemic control with similar safety and tolerability profiles. The proven once-daily DPP-4 inhibitor, sitagliptin, has been consistently demonstrated to produce significant reductions in HbA1c and fasting plasma glucose from the rich long-term international data base. Trelagliptin, on the other hand, has the unique benefit of being administered once a week, which could potentially increase patient adherence and convenience and improve treatment satisfaction without sacrificing benefit.

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