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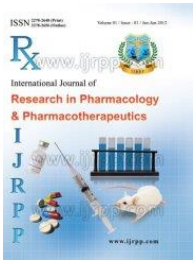

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Research article ***Open Access***

Comparison of efficacy and safety of teneligliptin versus sitagliptin as add on to metformin in type 2 diabetes mellitus at a tertiary care hospital

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ABSTRACT

Introduction

Diabetes mellitus (DM) is a leading cause of mortality and an increasing health burden with a prevalence of 8.3% globally and 9.1% in India (IDF). Prevention of complications and improving quality of life are the principle goals in its management. DPP-4 inhibitors have a potential vasoprotective effect mediated by stromal cell derived factor-1a. Teneligliptin a novel, highly selective, more potent agent compared to Sitagliptin provides sustained glycaemic control, decreases cardiovascular complications, has additional beneficial pleiotropic metabolic effects and also safe in renal impairment.

Objective

To evaluate the glycaemic and non-glycaemic effects of Teneligliptin vs Sitagliptin as add on therapy to metformin.

Materials and methods

After obtaining Institutional Ethics Committee approval and written informed consent, 60 subjects with T2DM who failed to achieve glycaemic control with metformin (500mg TID) alone for 3 months were randomized in 1:1 ratio to receive Teneligliptin 20mg OD and Sitagliptin 100mg OD as add on therapy. Patients were followed up at 4, 8 and 12 weeks for glycaemic and non-glycaemic effects. Adverse drug reactions (ADRs), if any were recorded and graded according to severity.

Results

There was a statistically significant decrease in FBS ($p<0.05$, $p<0.001$) and PPBS ($p<0.01$, $p<0.001$) in patients treated with Teneligliptin on week 8 & week 12 from baseline compared to those treated with Sitagliptin. The reduction in HbA_{1c} ($p<0.0001$), LDL-CH ($p<0.0001$) & TC ($p<0.001$) on week 12 from baseline was also significantly more in the Teneligliptin group.

Conclusion

Teneligliptin may be an effective and safe treatment option in reducing both glycaemic and non-glycaemic parameters as an add-on therapy in Type 2 DM with good patient tolerability.

Keywords: Teneligliptin, Type 2 DM, Sitagliptin, DPP4 Inhibitors.

INTRODUCTION

'It feels so sweet to have a healthy heart beat'. Diabetes mellitus (DM) a major lifestyle disease is undoubtedly the most challenging public health problem of 21st centuryand one of the leading causes of morbidity and mortality worldwide and a major problem in India. [1] The number of patients with type 2 DM is rapidly increasing worldwide, especially in the Asian countries, because of aging population and changes in dietary habits. [2] According to the Diabetes Atlas 2006 by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. [3]

Diabetes is managed using a stepwise approach involving lifestyle modifications, followed by addition of oral antidiabetes drugs such as metformin if HbA_{1C} level remains above 7.0%. [4] Despite initial monotherapy, majority of patients fail to achieve glycemic goals and may require combination therapy. Dipeptidyl peptidase (DPP)-4 inhibitors are a relatively new class of oral anti-hyperglycaemic drugs that have shown to improve beta cell function and/or neogenesis. [5] Due to the complementary mechanisms of action, a combination of metformin (decreases insulin resistance) with a DPP 4 inhibitor (improves beta cell function) helps in maintaining HbA_{1C} within the target range. [4]

DPP 4 inhibitors are considered to be more effective in Asian patients because diabetes is due to insufficient insulin production when compared to the Caucasians who usually have insulin resistance. [6] Previous studies have shown a reduction in HbA_{1C} by 0.6% by sitagliptin 100 mg/ day and 0.7% by teneligliptin 20 mg/day. [7, 8] Meta-analysis indicated DPP 4 inhibitors to have a beneficial effect on cholesterol that could contribute to reduction of cardiovascular risk. [9] Comparative inhibition studies showed teneligliptin exhibited more potent inhibition of DPP 4 enzyme than sitagliptin because of its unique J- shaped structure and anchor lock domain. [10]

Few studies have examined differences in control of glycaemic and non glycaemic parameters between different DPP4 inhibitors. In view of the limited body of studies between teneligliptin and sitagliptin, we conducted a randomized prospective comparative study using HbA_{1C} as the primary tool to investigate the blood glucose level.

MATERIALS AND METHODS

This was a randomized, open-label, comparative study conducted among 60 patients who attended the out-patient Department of Medicine in Bangalore Medical College and Research Institute, Bengaluru. After obtaining Institutional Ethics Committee approval and written informed consent, the patients who failed to respond to metformin 500 mg tid with adequate diet and exercise were randomized into 2 groups in a 1:1 ratio of 30 patients in each group and randomization done using the computer generated randomization sequence. Group 1 received teneligliptin 20 mg once daily, and group 2 received sitagliptin 100mg once daily. Concomitant medications like anti-hypertensives and lipid-lowering drugs were left unchanged during the study period. Patients of both groups were instructed to strictly maintain dietary habits and daily activities during the course of the study. They were assessed at the outpatient visit four times: at baseline, 4, 8 and 12 weeks. At baseline, blood samples for bio-chemical measurements were assessed and also repeated at follow up visits. Adverse drug reactions events if any were recorded in CDSCO-IPC form.

Selection criteria

Patients willing to give written informed consent of either sex, aged between 18 to 80 years, diagnosed with Type 2 DM according to ADA criteria, who did not achieve glycaemic target with metformin alone for 6 months and having HBA_{1C} levels between 7-9% on monotherapy with metformin 1.5g/day for 6 months prior to visit were included in the study. Patients who suffered an attack of acute coronary syndrome, transient ischaemic attack or stroke in the past three months, those with hepatic disease (serum level of ALT, AST, Alkaline phosphatase >3times the upper limit of normal), type 1 diabetes mellitus, severe ketosis, coma or reduced level of consciousness within the past 6 months due to diabetes, severe infection, pre or post operative, severe trauma, history of a chronic intestinal disease associated with absorption and digestive problems, moderate or severe renal dysfunction (creatinine clearance <50ml/min, serum creatine level >1.5mg/dl in men and 1.3mg/dl in females) or those with history of type 1 DM or secondary form of diabetes due to pancreatic diseases were excluded from the study.

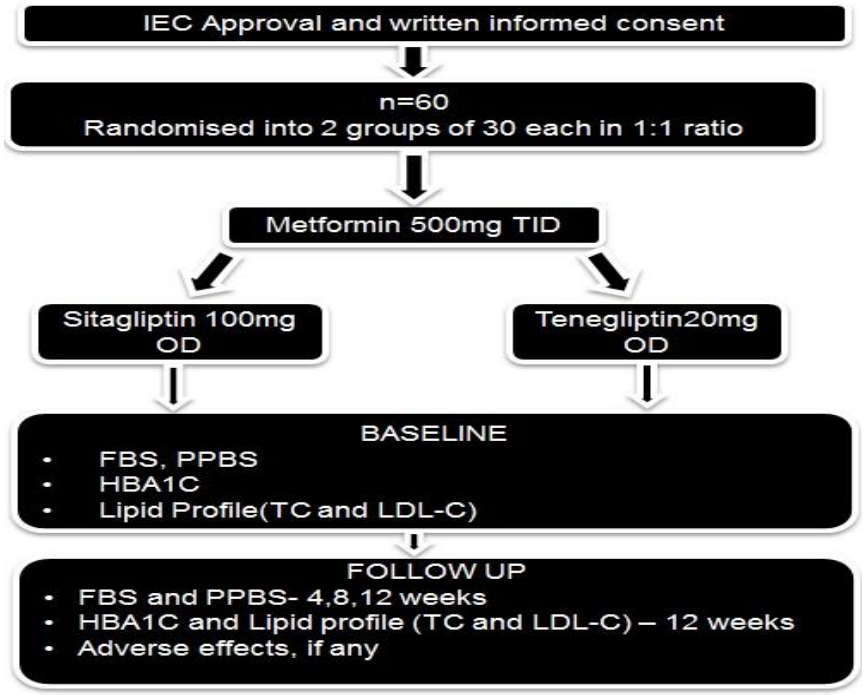


Figure 1: Study methodology

Statistical analysis

All categorical variables were represented in terms of percentage, continuous variables were represented in terms of mean ± standard deviation and inter and intra group comparisons was done using unpaired t-test and ANOVA respectively. The level of significance was set at $p<0.05$. Statistical analysis of data was performed using Vassar stats.

RESULTS

A total of 60 patients were included in the study. There was no statistical differences between both the groups at baseline with respect to demographic characteristics, glycaemic and non-glycaemic parameters. (Table 1)

Table 1: Baseline characteristics of patients

Characteristics	Teneligliptin	Sitagliptin	*p* value
Age in years (Mean±SD)	49.5+15.5	47.5+15.5	0.26
Gender	Male – 51% Female – 49%	Male – 54% Female – 46%	0.37
BMI (Mean±SD)	27.9±4.8	27.3±4.4	0.28
HBA_{1C} (Mean±SD)	8.8±0.35	8.4±0.42	0.18
FBS (Mean±SD)	170±5.5	168±5.5	0.39
PPBS (Mean±SD)	261±4.6	255±4.7	0.33
TC (Mean±SD)	226.4±32.25	229.9 ±30.1	0.24
LDL (Mean±SD)	165±30.17	154±27.11	0.05

Table 2: Mean reduction in glycemic and non- glycemic parameters in teneligliptin group

	Baseline	4 weeks	8 weeks	12 weeks	*p* value
FBS	170±5.3	148.1±3.2	138.5±2.1	130.1±1.9^{x}	0.001
PPBS	261.85±4.5	213.7±3.9	190±2.6	204±1.3**	0.03
HbA1c	8.8 ± 0.35	-	-	7.98±0.65#	0.002
TC	226.4±32.25	-	-	186.2±22.2$^{\$}$	0.001
LDL	165±30.1	-	-	130.7±19.1$^{\$\$}$	0.03

Table 3: Mean reduction in glycemic and non- glycemic parameters in Sitagliptin group

	Baseline	4 weeks	8 weeks	12 weeks	*p* value
FBS	168±5.5	149±1.4	145±2.2	145±1.7	0.003
PPBS	255±4.7	214.4±2.3	214.5±3.2	206.4±1.6	0.02
HbA1c	8.4±0.42	-	-	7.8±0.55	0.001
TC	229±30.1	-	-	217.4±24.6	0.002
LDL	154±27.11	-	-	152±19.8	0.04

FBS× *p- <0.001*
PPBS***p-<0.001*
HbA_{1C}*# p- <0.0001*
TC$^{\$}$ *p-<0.001*
LDL$^{\$\$}$ *p- <0.0001*

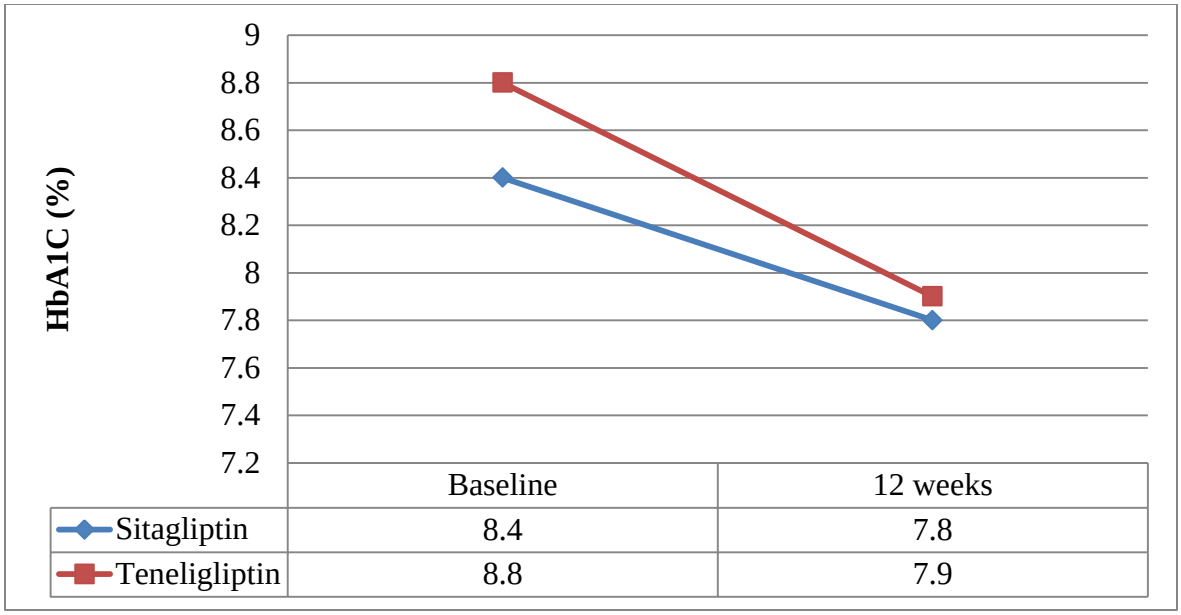
Table 4: Mean glycaemic parameters between 2 groups

	Teneligliptin	Sitagliptin	p value
FBS			
Baseline	170±5.3	168±5.5	0.39
4 weeks	148.1±3.2	149±1.4	0.40
8 weeks	138.5±2.1	145±1.2	<0.05
12 weeks	130.1±1.9	145±1.7	<0.001
PPBS			
Baseline	261.85±4.5	255±4.7	0.33
4 weeks	213.7±3.9	214.4±2.3	0.34
8 weeks	190±2.6	214.5±3.2	<0.01
12 weeks	204±1.3	206.4±1.6	<0.001
HbA1c			
Baseline	8.8±0.35	8.4±0.42	0.18
12 weeks	7.98±0.65	7.8±0.55	<0.0001

Table 5: Mean non-glycaemic parameters between 2 groups

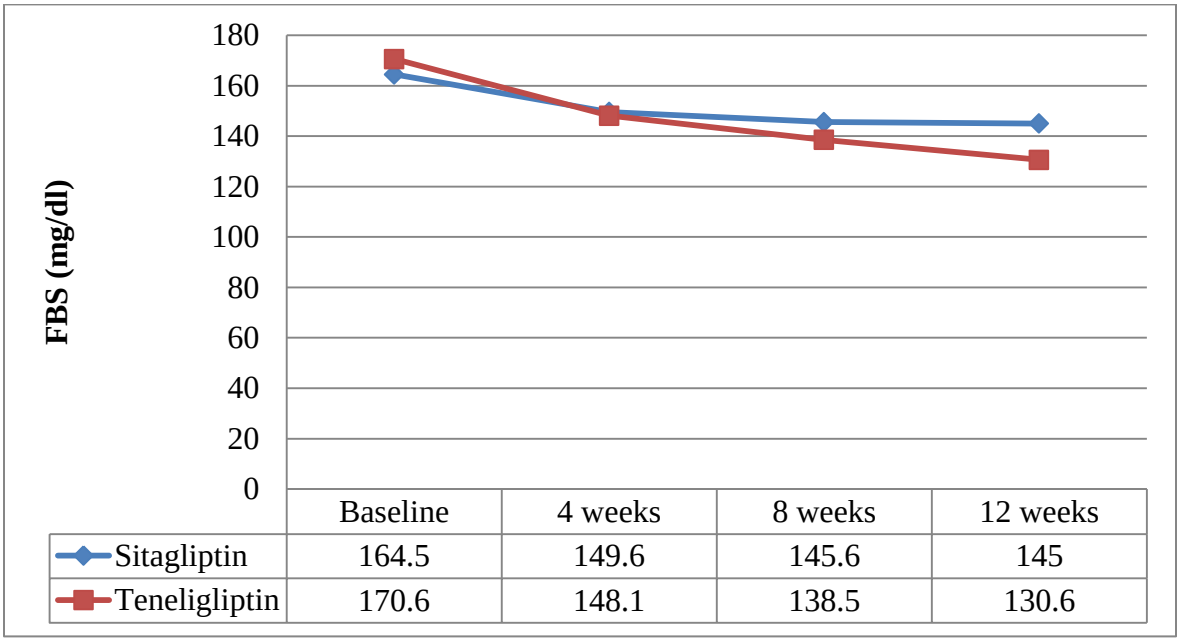
	Teneligliptin	Sitagliptin	p value
TC			
Baseline	226.4±32.25	229±30.1	0.24
12 weeks	186.2±22.2	217.4±24.6	<0.001
LDL			
Baseline	165±30.1	154±27.1	0.05
12 weeks	130.7±19.1	152±19.8	<0.0001

The change in HbA_{1C} from baseline was the most important primary end point of our study. At the end of 12 weeks of treatment, both groups had a decline in HbA_{1C} but the teneligliptin group had the greatest (0.9 ± 0.11 % vs 0.6 ± 0.14, *p*= <0.0001) [Graph 1]. The baseline FBS and PPBS values in both the groups were matched. There was a statistically significant decrease in FBS at end of week 8 (*p<0.05*) and week 12 (*p<0.001*) from baseline in patients treated with Teneligliptin compared to those treated with Sitagliptin [Graph 2]. The reduction in PPBS was also statistically significant at week 8 (*p<0.01),* and week 12 *(p<0.001*) in Teneligliptin group when compared to those treated with Sitagliptin [Graph 3].The total cholesterol (TC) and Low density lipoproteins (TC, LDL) were the non-glycaemic parameters assessed and followed up at week 12. Baseline values for non glycaemic parameters in both the arms were matched as tabulated in Table 1. At the end of 12 weeks though both the groups showed a downtrend, the decrease was higher in the teneligliptin group at the end of 12 weeks (TC: *p<0.001,* LDL: *p<0.0001*) as shown in Graph 4 and 5 respectively.



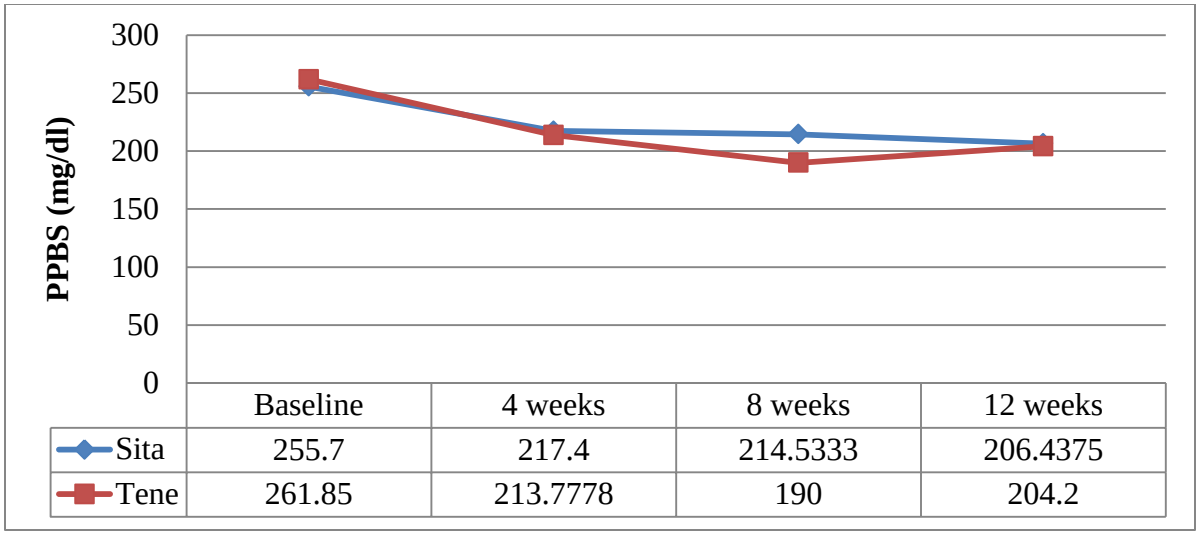
p<0.0001 at the end of 12weeks

Graph 1: HBA$_{1c}$ values



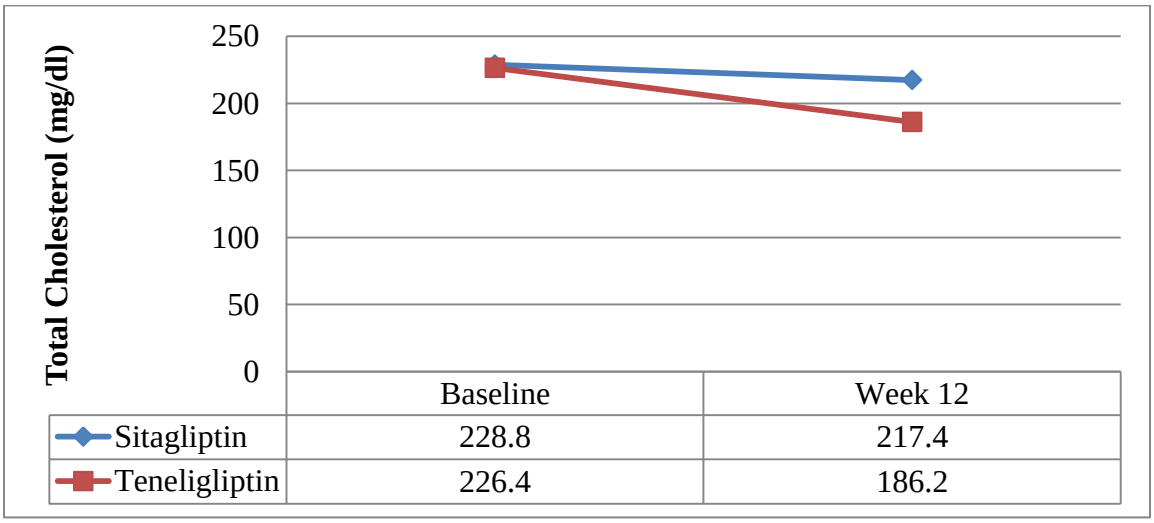
p<0.001 at the end of 8 weeks, p< 0.05 at the end of 12 weeks

Graph 2: FBS values

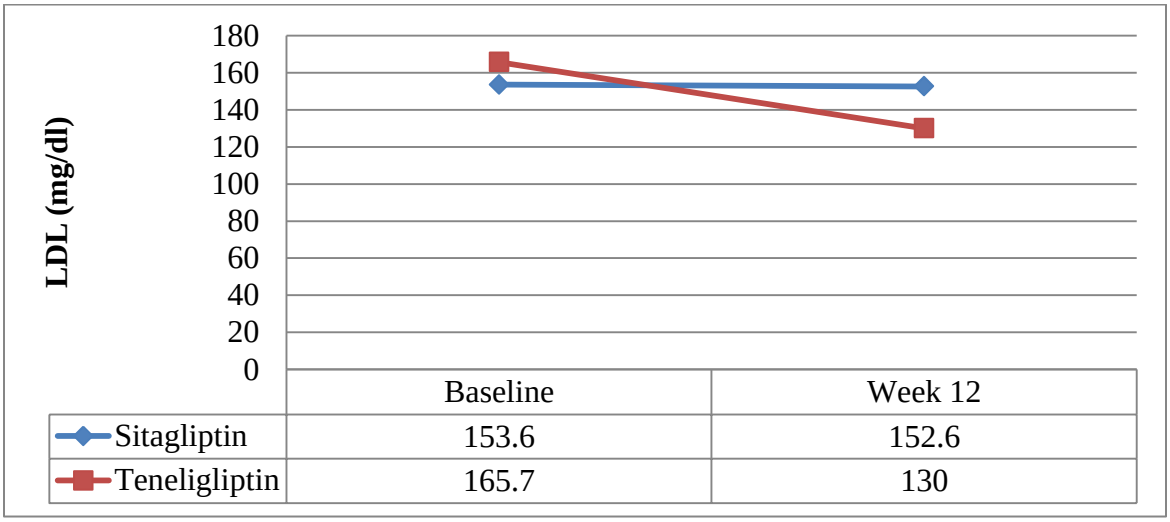


p<0.01 at week 8 and p<0.001 at week 12

Graph 3: PPBS values



Graph 4: Total cholesterol levels



Graph 5: LDL levels

The most common ADRs experienced in both groups were nausea, constipation and abdominal cramps, few patients also complained of joint pain and hypoglycemia. Across both the groups, no severe ADRs were recorded. Gastro-intestinal effects (nausea, constipation, abdominal cramps) were 15% in both groups, higher incidence of joint pain (10% Vs 5%) were seen in the teneligliptin arm and hypoglycaemia was seen only in the sitagliptin group.

Table 5: Adverse effects

Adverse effects	**Teneligliptin** (n=30)	**Sitagliptin** (n=30)
Gastro-intestinal side effects	15%	15%
Joint pain	10%	5%
Hypoglycaemia	None	5%

DISCUSSION

"Diabetes –the silent killer which kills part by part of our life". Diabetes, in all its forms, imposes high human, social & economic costs on countries at all income levels. [3] From a simple disease of insulin deficiency, to a bifactoral model of insulin deficiency & resistance, to a multifactorial condition, diabetes is a challenging proposition. [11] Over the years as the understanding of diabetes pathophysiology has evolved, there has been a tremendous improvement in the way we approach & manage this disease. The inability of therapy to maintain good glycemic control in T2DM is due to progressive deterioration of β-cell function, co-morbidities and infections. This provides the rationale for the early use of combination therapy with different class of drugs. Considering all these elements, the chosen therapeutic regimen must be balanced to achieve good glycemic control. [7]

Dipeptidyl peptidase-4 inhibitors, also called gliptins were one of the first classes of oral antidiabetic drugs to be prospectively designed as anti-hyperglycaemic agents, in contrast to other traditional agents,whose glucose-lowering effects were discovered serendipitously. [12] The classical mechanism of DPP-4 inhibitors is that these drugs increase the active levels of incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and thereby improving pancreatic α- and β cell sensitivity to glucose. [13]

Teneligliptin exhibits more potent inhibition of DPP4 enzyme than other gliptins. DPP-4 enzyme has five binding sites (subsites), namely, S1, S2, S1′, S2′, and S2 extensive. An interaction of DPP-4 inhibitors with S1 and S2 is fundamental for DPP-4 inhibition. Additional interaction with S1′, S2′, and S2 extensive site may further increase the DPP-4 inhibition. Both sitagliptin and teneligliptin are type 3 DPP 4 inhibitors that bind to additional site of S2 extensive, thereby producing more extensive inhibition. Teneligliptin has fivefold higher activity than sitagliptin, because of favorable (J-shaped) structure leading to small loss of energy during binding with DPP-4; formation of hydrogen bond with DPP-4 and due to more extensive binding at "S2 extensive" site than Sitagliptin. [14] Inhibition of the DPP-4 substrate by Teneligliptin involves formation of a reversible covalent enzyme–inhibitor complex that binds and dissociates from the catalytic site of the DPP-4 substrate very slowly resulting in persistent DPP-4 inhibition even after the drug is inactivated or the free drug has been removed from circulation. [15]

This 12-week, randomized, open-label, study evaluated the efficacy and safety of both glycaemic and non-glycaemic effects of teneligliptin and sitgliptin in Indian patients with T2DM inadequately controlled on metformin monotherapy with adequate diet control and physical activity.

T2DM was once considered a disease of older adults but the age of diagnosis is decreasing and it is now increasingly diagnosed in adolescents and young adults to the extent that T2DM will soon become the predominant form of diabetes in some ethnic groups. [16]

The mean age in teneligliptin and sitagliptin groups were 47.3+15.5 and 49.5+15.5 respectively which is similar to the results obtained from previous studies. In an Indian study by Gupta M et al, maximum number of people with diabetes was between 40-59 yrs of age. [1]

Gender-related differences in lifestyle may lead to differences in the risk of developing diabetes mellitus. Men seem more susceptible than women to the consequences of indolence and obesity, possibly due to differences in insulin sensitivity and regional fat deposition. T2DM showed a pronounced female

preponderance in the first half of the last century but is now equally prevalent among men and women in most populations, with some evidence of male preponderance in early middle age. [17] The results in the present study were in concordance with the above statement, showing male preponderance in middle age (54% in the teneligliptin group and 51% in the sitagliptin group).

In our study, both the groups achieved better glycaemic and non- glycaemic control when compared to the baseline, though teneligliptin group showed a superior decline. Our primary study end point was to assess the change in HbA_{1C}. At week 12, both the groups achieved significant reduction in HbA_{1C} with a greater decline in the Teneligliptin group (0.9 ± 0.11 % vs 0.6 ± 0.14, p= <0.0001). Dual therapy of Teneligliptin with metformin led to a significant HbA_{1C} reduction of 1.07% in studies conducted by Ghosh et al. [18] In a randomized, double-blind, placebo-controlled, parallel-group study by Kadowaki et al, patients (n = 324) were randomized to receive teneligliptin 10, 20 or 40 mg, or placebo, once daily before breakfast for 12 weeks. There was a 0.9% reduction in HbA1c with 20 mg teneligliptin which is similar to findings in present study. [19] Similar results were also obtained in a multicentre, randomized, phase III study in Korea. Teneligliptin significantly reduced the HbA1c level (0.94%) from baseline compared with placebo after 24 weeks. [20]

The percentage reduction in HbA1c in sitagliptin group was 0.6%. In a study conducted by Raz et al comparing sitagliptin with placebo, a significant reduction in HbA_{1C} from the baseline at the end of 12 weeks (0.60%) was seen, consistent with the above results. [8] In another study conducted by EuJeong et al, the efficacy of initial combination of sitagliptin with metformin in patients with a history of T2DM was assessed for a study time of 4 years. At the end of 4 years, HbA_{1C} levels significantly reduced (p<0.001). [21] Our study results were similar to above mentioned studies.

Both the groups showed statistically significant effect on glycemic control. The reduction in FBS values at week 8 and 12 was statistically significant in Teneligliptin group in comparison to sitagliptin group. Kutoh et al in a 3 month study of 31 drug naive Japanese T2DM patients, evaluated teneligliptin daily 20 mg as a monotherapy. This study found a significant reduction in fasting blood glucose (p<0.0002) at the end of 4 weeks from the baseline. [22] Similarly the teneligliptin group saw a significantly greater decline in PPBS at weeks 8 (HbA_{1C}: *p<0.01)* and 12 *(p<0.001)*. But the maximum change in PPBS was observed at week 8 (*p<0.01)*. In a Japanese study (n=99), teneligliptin 20 mg significantly reduced 2 h PPBS levels *(p<0.01)* against placebo at breakfast, lunch, and dinner at the end of 4 weeks. [23] The present study showed decrease in PPBS at 8 and 12 weeks.

Reports on the effects of DPP-4 inhibitors in improving insulin resistance and the serum lipid profile in humans are few. A meta-analysis suggested a possible beneficial effect of DPP-4 inhibitors on cholesterol which, although small, could contribute to the reduction of cardiovascular risk. [24] Kusunoki et al showed beneficial effect of Teneligliptin on lipid profile. 14-weeks treatment with Teneligliptin 20 mg/day showed significant improvement in lipid profiles. [25] It has been demonstrated that DPP4 stimulates lipid accumulation and PPAR-γ expression through cleavage of neuropeptide Y suggesting that DPP4 might stimulate adipocyte differentiation. On the contrary, recent published study showed that DPP4 expression was strongly upregulated during adipocyte differentiation in vitro. Hence, it has been concluded that DPP4 might be a major component in adipose tissue remodeling and cell plasticity. [26] In a meta-analysis, the treatment with DPP4 inhibitors determined a significant reduction of total cholesterol at the end of 24 weeks. [27]

In our study, reduction in TC and LDL which was higher in the teneligliptin arm probably is because of its more sustained inhibition of D2 enzyme. [28] The probable significant effect on non glycemic parameters require further evidence and longer duration of study to assess the significance of DPP 4 inhibitors on non glycemic parameters.

Assessment of ADRs was another important outcome of the study. Based on previous literature, the possible adverse effects encountered by gliptins are GI side effects, joint pain, infections and hypoglycaemia (rare). Gastro-intestinal side effects like abdominal pain and constipation are believed to be due to enhanced activity of incretins. [7] The adverse effects noted in our study were gastrointestinal side effects and joint pain. A single episode of mild hypoglycaemia was also noted in the sitagliptin group.The incidence of adverse events (AEs) was not significantly different between

teneligliptin and sitagliptin group in the present study.

After extensive literature search, to the best of our knowledge, the present study is the first to compare efficacy and safety of teneligliptin and sitagliptin as add on to metformin amongst Indian subjects. Randomisation of the study subjects and assessment of the effect on glycaemic and non glycaemic parameters added strength to the study.

The present study had certain limitations. The study was performed in a relatively small number of patients, open label study, LFT and long term effects of DPP4 inhibitors were not evaluated. Glycaemic variability (GV) measured using Continuous Glucose monitoring was not done adding to the limitation of the study.

During post-approval use of Teneligliptin therapy, adverse effects like hepatic dysfunction-associated cases were noted. Post-marketing reports of sitagliptin reported serious allergic reactions, including anaphylaxis, angioedema, and Stevens–Johnson syndrome. Additionally, close pharmacovigilance monitoring plans are necessary to address the uncertainty regarding AEs of DPP-4 inhibitors, while their potential impact on cardiovascular outcomes would be clarified in the near future after the completion of more relevant long-term studies.

It can be concluded that Teneligliptin, a potent DPP4 inhibitor with a long half-life and sustained DPP4 inhibition in comparison to sitagliptin has shown to decrease the fluctuations in glucose levels and suppress the post-prandial hyperglycaemia in type 2 DM patients. Teneligliptin 20mg OD significantly lowered the glycaemic and non-glycaemic parameters in comparison to sitagliptin 100mg OD. Teneligliptin serves as an appropriate add-on to Metformin early in therapy to delay exhaustion of pancreatic islet cell function and may be an effective and safe treatment option in type 2 DM with good patient tolerability.

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REFERENCES

[1]. Gupta M, Singh R, Lehl SS. Diabetes in India: a long way to go. Int J Sci Rep. 1(1), 2015, 1- 2.

[2]. Sakamoto M, Nishimura R, Irako T, Tsujino D, Ando K, Utsunomiya K. Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): crossover pilot study (J-VICTORIA study). Cardiovasc Diabetol. 2012, 11:92

[3]. International Diabetes Federation, World Diabetes Foundation. Diabetes atlas 2003. Brussels: International Diabetes Federation; 2003.

[4]. Deshmukh V, Sathyanarayana S, Menon S, Patil S, Jones R, Uppal S, et al. Safety and efficacy of initial combination of linagliptin and metformin in patients with type 2 diabetes: A subgroup analysis of Indian patients from a randomized, double-blind, placebo-controlled study. Indian J Endoc Metab. 19, 2015, 256- 61.

[5]. Balas B, DeFronzo RA. The Role of Dipeptidyl Peptidase-4 Inhibitors in the Management of Type 2 Diabetes. European endocrine disease 2, 2007, 45-50.

[6]. Goda M, Kadowaki T. Teneligliptin for the treatment of type 2 diabetes. Drugs Today (Barc) 49(10), 2013, 615-29

[7]. Maladkar M, Sankar S, Kamat K. Teneligliptin: Heralding Change in Type 2 Diabetes. Journal of Diabetes Mellitus. 6, 2016, 113-131.

[8]. Raz I, Hanefeld M, Xu L, Caria C, Herman DW, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 49, 2016, 2564-2571.

[9]. Monami M, Lamanna C, Desideri CM, Mannucci E. DPP-4 Inhibitors and Lipids: Systematic Review and Meta-Analysis.Adv Ther. 29(1), 2012, 14-25.

[10]. Rohrborn D, Wronkowitz N, Eckel J. DPP4 in diabetes. Front Immunol. 6, 2015, 386.

[11]. Kalra S, Das AK, Sahay R. Managing Diabetes: The Drivers of Change. Journal of Social Health & Diabetes. 1, 2013, 3-5.

[12]. Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase -4 inhibitors and sulphonylureas. Diabetes Obesity and Metabolism. 18, 2015, 333-347.
[13]. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes. 47(11), 1998, 1663-70.
[14]. Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S et al. A Comparative Study of the Binding Modes of Recently Launched Dipeptidyl Peptidase IV Inhibitors in the Active Site. Biochemical and Biophysical Research Communications. 434, 2013, 191-196.
[15]. Kushwaha RN, Haq W, Katti SB. Discovery of 17 Gliptins in 17-Years of Research for the Treatment of Type 2 Diabetes: A Synthetic Overview. Chemistry & Biology Interface. 4, 2014, 137-162.
[16]. Wilmot E, Idris I. Early onset type 2 diabetes: risk factors, clinical impact and management. Ther Adv Chronic Dis. 5(6), 2014, 234–244.
[17]. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev 37(3), 2016, 278-316.
[18]. Ghosh S, Trivedi S, Sanyal D, Modi K, Kharb S. Teneligliptin real -world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study).Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 9, 2016, 347–353.
[19]. Kadowaki T, Kondo K. Efficacy, safety and dose–response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Diabetes ObesMetab. 15(9), 2013, 810–818.
[20]. Hong S, Park CY, Han KA, Chung CH, Ku BJ, Jang HC et al. Efficacy and safety of teneligliptin, a novel dipeptidyl peptidase-4 inhibitor, in Korean patients with type 2 diabetes mellitus: a 24-week multicentre, randomized, double-blind, placebo-controlled phase III trial. Diabetes Obes Metab. 18(5), 2016, 528-32.
[21]. Eu JK, Kyong YJ, YoonJY, Kyoung MK, Jae HM, Sung HC et al. Four-Year Durability of Initial Combination Therapy with Sitagliptin and Metformin in Patients with Type 2 Diabetes in Clinical Practice; COSMIC Study. Plos one. 10(6), 2015, e0129477.
[22]. Eiji K, Mitsuru H, Yu I. Teneligliptin As an Initial Therapy for Newly Diagnosed, Drug Naive Subjects With Type 2 Diabetes. J Clin Med Res. 6(4), 2014, 287-294.
[23]. Eto T, Inoue S, Kadowaki T. Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: A 4-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 14, 2012, 1040–6.
[24]. Kishimoto M. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 6, 2013, 187-195.
[25]. Kusunoki M, Sato D, Nakamura T, Oshida Y, Tsutsui H, Natsume Y et al. DPP-4 Inhibitor Teneligliptin Improves Insulin Resistance and Serum Lipid Profile in Japanese Patients with Type 2 Diabetes. Drug Research. 65, 2015, 532-534
[26]. Rohrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. Frontiers in Immunology. 6, 2015, 386.
[27]. Monami M, Lamanna C, Desideri CM, Mannucci E. DPP-4 inhibitors and lipids: systematic review and meta-analysis. Adv Ther. 29(1), 2012, 14-25.
[28]. Zhong J, Gong Q, Goud A, Srinivasamaharaj Svidya S, Rajagopalan S. Recent Advances in Dipeptidyl-Peptidase-4 Inhibition Therapy: Lessons from the Bench and Clinical Trials. 2015, 2015, 1-14.