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RESEARCH ARTICLE

COMPARISON OF EFFICACY AND SAFETY OF TENELIGLIPTIN AND GLIMEPIRIDE AS ADD-ON TO METFORMIN IN AMELIORATING GLYCAEMIC VARIABILITY BASED ON PROFESSIONAL CONTINUOUS GLUCOSE MONITORING DATA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Glycemic variability takes into account the intraday glycemic excursions including episodes of hyper and hypoglycaemia. This study was planned to compare effects of teneligliptin and glimepiride as add-on to metformin on glycemic variability in Indian patients with uncontrolled type 2 diabetes mellitus (T2DM). **Methods:** This was a prospective, randomized, open-label, multi-centre study in 52 T2DM patients uncontrolled on optimal metformin dose (HbA1c 7.0%-9.5%). They were randomised in 1:1 ratio to teneligliptin 20 mg once daily (T/M group) or glimepiride(G/M group) as an add-on to metformin and were deployed with a professional continuous glucose monitoring (iCGM) device for 14 consecutive days. The endpoints measured were 24 hours mean glucose level, proportion of time in euglycemia (>70 - <180 mg/dL), hyperglycemia (>180 mg/dL), and hypoglycemia (< 70 mg/dL). **Results:** Significantly higher proportion of time was spent in hypoglycemia in G/M group compared to T/M group (10.04% vs 03.4%; p = 0.04). Proportion of time spent in euglycemia and hyperglycemia was comparable between the groups. There was greater reduction in PPG from baseline at Day 14 in T/M group (-27.16 ± 64.30 mg/dL) compared to G/M group (-7.19 ± 78.45mg/dL, p = 0.53). **Conclusion:** Teneligliptin as add-on to metformin offers low intraday glycemic variability, allowing more predictable glycemic control as compared to glimepiride and emerges as a safe, tolerable and effective treatment in patients with T2DM on more stringent criteria of glycemic variability.

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INTRODUCTION

The prevalence of diabetes has nearly tripled in the last 30 years (Stulc, 2010). Around 425 million people across the globe are living with diabetes and it is predicted that by 2045, this number shall rise to 629 million (IDF, 2017). Approximately two-thirds of patients with type 2 diabetes mellitus (T2DM) in developed countries do not effectively control their glucose levels and that an even greater proportion does not do so in developing countries. Given the huge burden T2DM poses on public health system, it calls for prompt intervention to improve the glycemic control so as to avert its short and long-term complications.

It also calls for focus on new parameters like glycaemic variability (GV) in addition to traditional end points like glucose levels and glycated haemoglobin (Satya Krishna, 2013). Most clinical practice guidelines (IDF Diabetes Atlas, 2015; American Diabetes Association, 2010; Consoli, 2004 Rojas, 2013), recommend metformin as the first-line oral anti-diabetic drug (OAD) for treating T2DM. T2DM is a progressive disorder and as patients continue to experience decline in β -cell function and worsening of insulin resistance, demand for add-on OADs ensues. Sulphonylureas (SU) had been a preferred option as add-on to metformin. However, with the availability of newer OADs with benefits of low risk of hypoglycaemia and weight neutrality, a clinical dilemma arises

while selecting SU as the second line treatment option. SUs have been shown to expedite beta-cell failure and induce apoptosis at rates greater by two to fourfold (Sawada, 2018 and Maedler, 2005). This precedes the future risk of early insulin dependence, high prevalence of hypoglycaemia, weight gain, and an increased incidence of cardiovascular events (Liu, 2012; Currie, 2013 and Phung, 2013). On the other hand, newer OADs like DPP4 inhibitors, as a class, have shown to preserve beta-cell function, have weight neutrality or even induce weight loss, and have a low intrinsic risk of hypoglycaemia (Lyu, 2017 and Amori, 2007) since they act in a glucose dependant manner. The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), European Society, and NICE (UK) guidelines suggest that gliptins should be considered over other oral anti-diabetic therapies after metformin especially if the patient is experiencing an increased incidence of hypoglycemia and/or weight gain (Rodbard, 2009; Nathan, 2009 and 17. NICE, 2018). Maladkar *et al.* (2016) mentioned in their comprehensive review that teneligliptin serves as an appropriate add-on to metformin early in therapy to delay exhaustion of pancreatic islet function. Teneligliptin, a third generation gliptin, is a Class 3 inhibitor with reported fivefold higher activity than sitagliptin (Nabeno, 2013). Its unique “J-shaped anchor-lock domain” provides potent and long duration of action. Further, it has a unique structure and binds to S1, S2, and S2 extensive subsite of DPP-4 enzyme which leads to enhanced potency and selectivity (Nabeno, 2013 and 21. Yoshida, 2012). It also possess other important clinically significant properties like once-a-day administration, maximum inhibition of DPP-4 enzyme within 2 hours, 24 hours glycemic control, minimal drug–drug interaction and elimination by renal and hepatic route (Kishimoto, 2013 and Eto, 2012). It has insulinotropic, glucagonostatic and β -cell salvager properties.

In countries like India, as SUs and DPP4 inhibitors are preferred as the most cost-effective option as add-on to metformin, this study was planned to compare the glycaemic variability with the commonly used SUs and DPP4 inhibitors; glimepiride and teneligliptin respectively. Most of the previous studies relied on self-reported hypoglycaemia and self-monitoring of blood glucose (SMBG) as indicators of glycaemic variability. For better predictability, we compared the effects of teneligliptin and glimepiride as add-on to metformin on glycaemic variability in Indian patients with T2DM by analysing 24-h glycaemic fluctuations, retrospectively. For this, we utilized a professional continuous glucose monitoring (iCGM) system to provide information about the frequency of glycaemic fluctuations. The present study is the first of its kind reporting on effects of teneligliptin plus metformin on glycaemic variability from Indian population, and third only, worldwide after two Japanese studies of very small sample size ($n=26$ and $n=10$, respectively) (Tanaka, 2014 and Tsuchimochi, 2015).

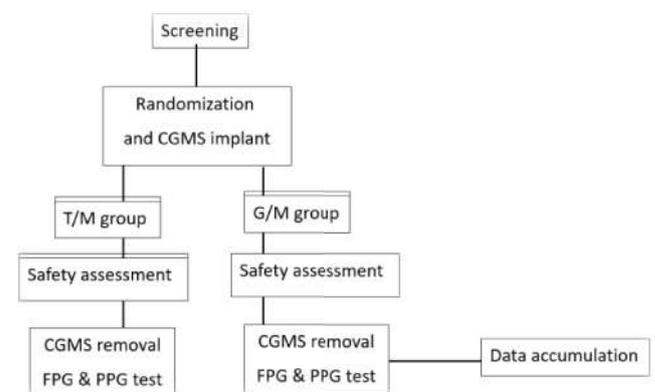
MATERIAL AND METHODS

Subjects: This was a prospective, randomised, open-label, multi-centre, controlled clinical trial of 52 T2DM patients aged 30–79 years, who had inadequate glycaemic control (HbA1c above 7.0% and below 9.5%) in spite of optimal metformin dose, along with diet and exercise. Exclusion criteria were: i. type 1 diabetes ii. serious infection iii. patients with QT prolongation, arrhythmia or related risk due to underlying

cardio-vascular diseases iv. pre or post-operative condition, or severe trauma v. pregnancy, woman of child bearing age not using contraceptive methods, breast-feeding vi. Moderate or severe renal dysfunction (estimated glomerular filtration ratio [mL/min/1.73 m²]) < 50 mL/min, or serum creatinine level > 1.5 mg/dL in men or > 1.3 mg/dL in women) vii. Severe liver dysfunction viii. Insulin treated patients ix. Treatment with oral anti-diabetic agents except metformin x. history or risk of acute pancreatitis. Patients were given detailed explanations of the study protocol. Those who provided written informed consent were included in the study. The study protocol was approved by the Ethical Committee. The study was conducted based on Declaration of Helsinki.

Methods

Study schematics are depicted in Figure 1.



CGMS – continuous glucose monitoring system, T/M – metformin + teneligliptin, G/M – metformin + glimepiride, FPG – fasting plasma glucose, PPG – post-prandial plasma glucose

Figure 1. Study schematics

Total 52 eligible consecutive patients were randomized in 1:1 ratio to either of the two arms (metformin + teneligliptin [T/M] or metformin + glimepiride [G/M]). One of the treatment groups received tablet teneligliptin 20mg once daily before breakfast, and other group received tablet glimepiride at standard dose as an add-on to metformin, for 14 days. They underwent thorough clinical examination with assessment of medical history and demographics. Patients of both the treatment arms were deployed with iCGM device for 14 consecutive days. Each patient was monitored throughout the study period for any adverse drug reaction. Administration of other OADs was prohibited during the study period and in case, rescue medications were required, they were to be prescribed at the discretion of the clinician and the subject was to be discontinued from the study. The primary endpoints measured were 24-hours mean glucose level (mg/dL), proportion of time in euglycemia (blood glucose >70 - <180 mg/dL), hyperglycemia (blood glucose >180 mg/dL), and, hypoglycaemia (blood glucose < 70 mg/dL). Secondary endpoints were change in fasting and post-prandial glucose level from baseline, and adverse events if any. The subjects ingested near identical meals, and were advised not to change their level of exercise during the study period.

Statistical analysis

Data were expressed as mean \pm standard deviation. The student t-test and chi square test were used to compare values between two groups, with the level of significance set at $p < 0.05$.

Statistical analysis of data was performed using the Statistical Package for Social Sciences software, version 10.0 (SPSS, Chicago, IL, USA).

RESULTS

The patient demographics are shown in table 1. Total 28 patients were analysed in T/M group and 24 patients in G/M group. The groups were comparable at baseline with respect to age and body mass index (BMI) (Table 1). Average 24-h blood glucose was higher in T/M group (174.79 ± 25.93) compared to G/M group (159.73 ± 36.37). As shown in Table 2, proportion of time spent in euglycemia was slightly higher in G/M group compared to T/M group, but difference was not statistically significant ($p = 0.38$). Significantly higher proportion of time was spent in hypoglycemia in G/M group compared to T/M group ($p = 0.04$). Numerically higher proportion of time was spent in hyperglycemia in T/M group compared to G/M group but the difference was not statistically significant ($p = 0.06$). Table 3 shows the minimum and maximum blood glucose levels recorded in both groups during the entire study period.

Mean FPG and PPG were comparable at baseline between the groups (Table 4). There was significant reduction from baseline in FPG in G/M group (-23.88 mg/dL, $p = 0.02$) at Day 14. Reduction in FPG from baseline at Day 14 in T/M group was not statistically significant (-15.33 mg/dL, $p = 0.26$). Numerically, the decrease in FPG was less in T/M group than in G/M group but the difference was not statistically significant ($p = 0.66$). There was greater reduction in PPG from baseline at Day 14 in T/M group (-27.16 mg/dL) compared to G/M group (-7.19 mg/dL) but the difference was not statistically significant ($p = 0.53$).

DISCUSSION

Efficacy of anti-hyperglycemic interventions is often at odds with hypoglycemia. Previous studies relied on self-reported hypoglycaemia but the incidence of asymptomatic hypoglycemia went unrecognized. Glycemic variability (GV) is an endpoint which takes into account the intraday glycemic excursions including episodes of hyper and hypoglycaemia. These peaks and nadirs of glycemic levels are responsible for various microvascular and macrovascular complications in

Table 1. Demographic characteristics of type 2 diabetes patients treated with teneligliptin or glimepiride as add-on to metformin

Parameters	T/MGroup (n=28)	G/MGroup (n=24)	P Value
Age (years)			0.55
Mean (\pm SD)	58.59 \pm 08.75	56.96 \pm 10.44	(NS)
Range	41.0– 73.0	32.0 – 73.0	
BMI (Kg/m ²)			0.72
Mean(\pm SD)	25.63 \pm 02.87	25.75 \pm 02.31	(NS)
Range	20.5 – 33.9	21.6 – 31.7	
Sex (%)			0.30
Male	18 (64.3)	12 (50.0)	(NS)
Female	10 (35.7)	12 (50.0)	

By Student t test, Chi - Square Test, NS = Not Significant

Table 2. Comparison of Average Blood Glucose, Proportion of Time in Euglycemia, Hyperglycemia and Hypoglycaemia in patients treated with T/M and G/M

Parameter	Treatment Groups		P value
	T/M Group	G/M Group	
Proportion of Time in Euglycemia (%) (blood glucose >70 - <180 mg/dL)	30.14	34.14	0.38 (NS)
Proportion of Time in Hypoglycemia (%) (blood glucose < 70 mg/dL)	03.40	10.04	*0.046
Proportion of Time in Hyperglycemia (%) (blood glucose >180 mg/dL)	66.46	55.82	0.06 (NS)

By Student t test, NS = Not Significant, *Significant, T/M - metformin + teneligliptin, G/M - metformin + glimepiride

Table 3. Comparison of Highest and Lowest Glucose Level Recorded (14 Days)

Parameter	T/M Group (mg/dL)	G/M Group (mg/dL)
Minimum Glucose Level	73	40
Maximum Glucose Level	287	320

T/M - metformin + teneligliptin, G/M - metformin + glimepiride

Table 4. Comparison of Changes in Mean Fasting and Post-prandial Blood Glucose from Baseline

Visit	Fasting Blood Glucose (m/dL) (mean \pm SD)			Post-prandial Blood Glucose (m/dL) (mean \pm SD)		
	T/M Group (n = 28)	G/M Group (n = 24)	P value	T/M Group (n = 28)	G/M Group (n = 24)	P value
Baseline	154.17 \pm 51.17	159.55 \pm 58.78	0.89 (NS)	191.99 \pm 59.37	181.75 \pm 65.88	0.75 (NS)
Day 14	145.14 \pm 38.10	133.58 \pm 40.68		172.35 \pm 51.99	162.75 \pm 64.33	
Change from baseline	-15.33 \pm 54.31 (0.26) NS	-23.88 \pm 41.26 (0.02)	0.66 (NS)	-27.16 \pm 64.30 (0.054)	-07.19 \pm 78.45 (0.12) NS	0.53 (NS)

By Student t test, *Significant, NS = Not Significant, T/M - metformin + teneligliptin, G/M - metformin + glimepiride

Diabetes (Stratton, 2000; Raz, 2009; Kota, 2011 and Kota, 2012). Hence, accurate determination of blood glucose concentrations is a prerequisite for the development of more efficacious therapeutic interventions. The present study is one of the first studies from India reporting on professional CGM monitored 24-hour glucose levels over a period of 14 days as an efficacy endpoint of teneligliptin added to metformin. Professional CGMs can provide actionable information based on changing interstitial fluid glucose levels in a retrospective manner and highlight glycemic fluctuations and trends that would not have been identified with the conventional self-monitoring of blood glucose alone. CGM has made the attainment of near-normal blood glucose concentrations an achievable goal and has also allowed the selection of lower target levels for mean glucose and HbA1c (Rodbard, 2017; Kesavadev, 2017 and Kesavadev, 2017). This has been further endorsed by the fact that CE (Conformite Europeenne) and US FDA (U S Food and Drug Administration) have recently approved CGM for adjustment of insulin dosages. Previous studies have been conducted in other ethnicities evaluating impact of gliptins on glycemic variability. As per Kim *et al.* (2013) the glucose-lowering effect of DPP-4 inhibitors appears to be greater in Asians compared with Caucasians. However, the impact on glycemic variability of DPP-4 inhibitors added to metformin need to be clarified in the Asian population. More so, Indians have a different meal pattern, physique and basal metabolic index compared to westerners and other Asians. Thus, this study answers an important research question.

In this study, the parameter of 'time in euglycemia' and 'time in hyperglycemia' were similar in both the groups, but 'time in hypoglycemia' was significantly lesser in T/M group than G/M group. It means that treatment with teneligliptin poses lesser risk of hypoglycemia to patients than treatment with glimepiride as add-on to metformin. At the end of 14 days, there was greater reduction in PPG in T/M group compared to G/M group. Our results are in agreement with other studies evaluating GV in T2DM patients receiving gliptins based on CGMS. A 4-week randomized, double-blind, prospective study by Kim *et al.*³⁴ compared the effects of sitagliptin and glimepiride on glycemic change and 24-h blood glucose variability as add-on to metformin. They concluded that in terms of conventional glycemic parameters like HbA1C, the two groups were similar, but the marker of glycemic variability, mean amplitude of glycemic excursions (MAGE) decreased significantly in the sitagliptin group (4.9 ± 1.0 to 3.7 ± 0.9 mmol/L, $P < 0.001$), but no significant difference was observed in the G/M group (5.7 ± 1.5 to 5.0 ± 1.4 mmol/L, $P = 0.175$).

In STABLE study which was a multicenter, randomized, active-controlled, open-label exploratory study conducted by Park S E *et al.* (2017), the effect of gemigliptin 50 mg ($n = 24$), sitagliptin 100 mg ($n = 23$) or glimepiride 2 mg ($n = 22$) as initial combination therapy with metformin on glycaemic variability was evaluated in 69 patients with HbA1c $> 7.5\%$. The researchers found that after 12 weeks, the change in MAGE compared with baseline was significantly lower in the DPP-4 inhibitor groups compared with that in patients who received glimepiride. Similarly, in another study conducted by Scherbaum *et al.* (2008), there was a significant decrease in glucose Area Under Curve (AUC 0-2 h) after 2 year treatment with vildagliptin than in placebo group. Interestingly, the study had also showed better effects in FBG and PPG as well as

improvement in β -cell function over 2 year treatment period in patients with T2DM. This additional benefit might be observed after long duration of administration. In a study conducted by Kesavadev *et al.* (2017), in Asian Indians with T2DM, sitagliptin (100 mg) when compared to glimepiride (1-3 mg), bestowed beneficial effects to the patients in terms of achieving greater glycaemic control and also brought significant reductions in total daily dose of insulin required, bodyweight, BMI and hypoglycemic events. The results indicated that sitagliptin is a superior agent over glimepiride as an add-on to insulin-metformin therapy. The results of present study indicate that the teneligliptin is equivalent to glimepiride in terms of FPG, PPG values and 24-hour glycemic levels, but scores higher in terms of safety related to hypoglycaemia. This is further emphasized by the fact that significantly higher time was spent in hypoglycemia in G/M group compared to T/M group ($p = 0.04$) and the lowest recorded glucose level was 40mg/dL, in T/M group and 73 mg/dL in G/M group. Further, the highest glucose excursion of 320 mg/dL was observed in G/M arm, while in T/M arm it was 287mg/dL. The average glucose level and percentage of time in target blood glucose levels were not significantly different among the two groups. The reason for this is that sulfonylurea's stimulation of insulin secretion is not strictly glucose dependent; they continue to stimulate insulin secretion even with falling glucose concentrations (Inzucchi, 2002). By contrast, teneligliptin inhibits the enzymatic degradation of glucagon-like peptide-1 (GLP-1), which in turn stimulates insulin secretion and inhibits glucagon release in a glucose-dependent fashion (Maedler, 2005). Similarly, comparable efficacy between gliptins and sulfonylureas when either is added to metformin has been proved in different meta-analyses. In terms of safety related to risk of hypoglycemia, cardiovascular events, and weight gain, gliptins score over sulfonylureas when used both as monotherapy or as add-on to ongoing metformin therapy (Ou, 2015). It is notable that teneligliptin also significantly decreased PPG in a short period of two week of administration in T2DM patients maintained only on metformin. Similarly, a Japanese study⁴⁴ had shown that once daily teneligliptin administration for 3 days significantly lowered PPG and FPG levels, 24 h mean blood glucose levels, standard deviation of 24 h glucose levels and MAGE without hypoglycemia. The ideal approach for T2DM management should be well rounded taking not only glycemic control into consideration, but also early preservation of isletfunction and providing a flat glycemic profile round the clock, a strategy currently used to delay progression of a T2DM. Given these properties, teneligliptin serves as an appropriate add-on to metformin early in therapy to delay exhaustion of pancreatic isletfunction (Maladkar, 2016).

Strengths and Limitations of the study: This study has certain limitations which should be considered when reviewing the results. First, the number of subjects enrolled was relatively small. However, the number of subjects is similar to some of the previous studies (Mori, 2011; Osonoi, 2014 and Kim, 2013), evaluating glucose fluctuations affected by antidiabetic drugs using CGM. Therefore, 24 and 28 patients in both arms respectively might be enough to verify the effects of teneligliptin on glucose fluctuation using CGM in present study. Secondly, data were collected only for duration of two weeks, so there are limitations in commenting on durability of the treatment. Lastly, metformin dosing was as per the treating physician's discretion, and overall efficacy may be impacted by the aggressiveness of the use of either drug. However, the

differential dosing reflects every day clinical use and suggests how patients will be treated outside of a research study.

Future Prospects: It should be noted that the limitations of our study include the small number of cases and the short duration of the period of investigation. Thus, for future studies, the durability of effects of the combination of teneligliptin with metformin needs to be explored as well as more detailed mechanistic studies need to be undertaken, vis-a-vis glucagon secretion, prandial lipid levels and insulin sensitivity.

Conclusion

To attain good “quality” of glucose control with reduced glycemic variability is a new end point on which modern T2DM therapies are being assessed. Our study has demonstrated that teneligliptin, when used as part of dual therapy with metformin, offers the potential for additional benefit accruing from reduced glycemic variability and the patients spend lesser time in hyperglycemia or hypoglycaemia. We conclude that teneligliptin added to metformin offers a flatter glycemic profile with low within-day variability, allowing a more predictable glycemic control. This effect was seen rapidly after administration of teneligliptin. Thus, teneligliptin added to metformin emerges as a safe, tolerable and effective treatment in management of patients with type 2 diabetes, on more stringent criteria of glycemic variability.

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Conflict of Interest – None.

Key Points

- Teneligliptin with metformin ensures good quality of glucose control with reduced glycemic variability in T2DM patients.
- Teneligliptin offers a more predictable glycemic control as compared to glimepiride.
- Teneligliptin added to metformin emerges as a safe, tolerable and effective treatment in management of patients with T2DM, on more stringent criteria of glycemic variability.

REFERENCES

- American Diabetes Association. Standards of medical care in diabetes - 2010. *Diabetes Care*. 33(Suppl 1): S11–S61. 2010.
- Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007; 298:194–200. doi: 10.1001/jama.298.2.194.
- Consoli A, Gomis R, Halimi S, Home PD, Mehnert H, Strojek K, *et al*. Initiating oral glucose-lowering therapy with metformin in type 2 diabetic patients: an evidence-based strategy to reduce the burden of late-developing diabetes complications. *Diabetes Metab*. 2004;30:509-16.
- Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin EndocrinolMetab*. 2013;98(2):668–77. doi: 10.1210/jc.2012-3042.
- Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. *Diabetes ObesMetab*. 2016;18(4):333–347.
- 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 ObesMetab*. 2012;14(11):1040–1046.
- Foroutan N, Muratov S, Levine M. Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: systematic review and meta-analysis. *Clin Invest Med*. 2016; 39(2):E48–E62.
- IDF Diabetes Atlas. 6th ed. International Diabetes Federation; 2015
- IDF. IDF Diabetes Atlas. 8th Edn. Brussels, Belgium: International Diabetes Federation; 2017.
- Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA*. 287:360–372. 2002.
- Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ*. 2012;344:e1369.
- Kesavadev J, Pillai PB, Shankar A, Krishnan G, Jothydev S. Sitagliptin 100 mg vs glimepiride 1-3 mg as an add-on to insulin and metformin in type 2 diabetes. *Endocrine connections*. 2017 Oct 5:EC-17..
- Kesavadev J, Ramachandran L, Krishnan G. Glucose monitoring technologies - complementary or competitive? Role of continuous glucose monitoring versus flash glucose monitoring versus self-monitoring of blood glucose. *Journal of Diabetology*. 2017;8(3):61-7.
- Kesavadev J, Vigersky R, Shin J, Pillai PBS, Shankar A, Sanal G, *et al*. Assessing the Therapeutic Utility of Professional Continuous Glucose Monitoring in Type 2 Diabetes Across Various Therapies: A Retrospective Evaluation. *Adv Ther*. 2017;34(8):1918-27
- Kim HS, Shin JA, Lee SH, *et al*. A comparative study of the effects of a dipeptidyl peptidase-IV inhibitor and sulfonylurea on glucose variability in patients with type 2 diabetes with inadequate glycemic control on metformin. *Diabetes Technol Ther* 2013;15:810–816.
- Kim HS, Shin JA, Lee SH, Kim ES, Cho JH, Son HY, *et al*. A comparative study of the effects of a dipeptidyl peptidase-IV inhibitor and sulfonylurea on glucose variability in patients with type 2 diabetes with inadequate glycemic control on metformin. *Diabetes Technol Ther*. 2013 Oct;15(10):810-6.
- Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. *Diabetologia*. 2013; 56: 696–708.
- Kishimoto M. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes*. 2013;6:187–195.
- Kota SK, Kota SK, Jammula S, Panda S, Modi KD. Effect of diabetes on alteration of metabolism in cardiac myocytes: therapeutic implications. *Diabetes Technol Ther*. 2011;13:1155–60.
- Kota SK, Meher LK, Jammula S, Kota SK, Krishna SV, Modi KD. Aberrant angiogenesis: The gateway to diabetic complications. *Indian J Endocrinol Metab*. 2012; 16:918–30.

- Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab*. 2012;14(9):810–20. doi: 10.1111/j.1463-1326.2012.01606.x.
- Lyu X, Zhu X, Zhao B, et al. Effects of dipeptidyl peptidase-4 inhibitors on beta-cell function and insulin resistance in type 2 diabetes: meta-analysis of randomized controlled trials. *Scientific Reports*. 2017;7:44865. doi:10.1038/srep44865.
- Maedler K, Carr RD, Bosco D, et al. Sulfonylurea induced beta-cell apoptosis in cultured human islets. *J Clin Endocrinol Metab*. 90:501–506. 2005.
- Maedler K, Carr RD, Bosco D, Zuellig RA, Berney T, Donath MY. Sulfonylurea Induced Beta-Cell Apoptosis in Cultured Human Islets. *The Journal of Clinical Endocrinology & Metabolism*, 2005; 90, 501-506.
- Maladkar M, Sankar S, Kamat K. Teneligliptin: Heralding change in type 2 Diabetes. *J Diabetes Mellitus*. 2016;6(2):113-31.
- Maladkar M, Sankar S, Kamat K. Teneligliptin: Heralding change in type 2 Diabetes. *J Diabetes Mellitus*. 2016;6(2):113-31.
- Mori Y, Taniguchi Y, Matsuura K, et al. Effects of sitagliptin on 24-h glycaemic changes in Japanese patients with type 2 diabetes assessed using continuous glucose monitoring. *Diabetes Technol Ther* 2011;13:699–703.
- Nabeno M, Akahoshi F, Kishida H, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. *BiochemBiophys Res Commun*. 2013;434(2):191–196.
- Nabeno M, Akahoshi F, Kishida H, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. *BiochemBiophys Res Commun*. 2013;434(2):191–196.
- Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of The American Diabetes Association and the European Association for the study of diabetes. *Diabetes Care*. 2009;32:193–203.
- NICE diabetes treatment algorithm. [Last accessed on 2018 Feb 27]. Available from: <http://www.nice.org.uk/guidance/CG66>.
- Osonoi T, Saito M, Tamasawa A, et al. Effects of sitagliptin or mitigliptide as an add-on to acarbose on daily blood glucose fluctuations measured by 72 h subcutaneous continuous glucose monitoring in Japanese patients with type 2 diabetes: a prospective randomized study. *Expert Opin Pharmacother* 2014;15:1325–1335.
- Ou SM, Shih CJ, Chao PW, et al. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med*. 2015;163(9):663–672.
- Park SE, Lee BW, Kim JH, Lee WJ, Cho JH, Jung CH et al. Effect of gemigliptin on glycaemic variability in patients with type 2 diabetes (STABLE study). *Diabetes Obes Metab*. 2017 Jun;19(6):892-896.
- Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. *Diabet Med*. 2013;30(10):1160–71. doi: 10.1111/dme.12232.
- Raz I, Wilson PW, Strojek K, Kowalska I, Bozikov V, Gitt AK, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: The HEART 2D trial. *Diabetes Care*. 2009;32:381–6.
- Rodbard D. Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes. *Diabetes Technology & Therapeutics*. 2017; 19(Suppl 3):S-25-S-37. doi:10.1089/dia.2017.0035.
- Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. *Endocr Pract*. 2009; 15:540–59.
- Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol MetabSyndr*. 2013;5:6. [PMID: 23415113] doi:10.1186/1758-5996-5-6
- Satya Krishna SV, Kota SK, Modi KD. Glycemic variability: Clinical implications. *Indian Journal of Endocrinology and Metabolism*. 2013;17(4):611-619. doi:10.4103/2230-8210.113751.
- SawadaF, Inoguchi T, Tsubouchi H, Sasaki S, Fujii M, Maeda Y, Morinaga H, Nomura M, Kobayashi K, Takayanagi R. Differential Effect of Sulfonylureas on Production of Reactive Oxygen Species and Apoptosis in Cultured Pancreatic Beta-Cell Line, MIN6. *Metabolism*. 2018; 57, 1038-1045.
- Scherbaum WA, Schweizer A, Mari A, Nilsson PM, Lalanne G, Wang Y, et al. Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycemia. *Diabetes ObesMetab*. 2008;10:1114–24
- Stratton IM, Adler AI, Neil HA, Mathews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*. 2000;321:405–12.
- Stulc T and Sedo A: Inhibition of multifunctional dipeptidyl peptidase-IV: is there a risk of oncological and immunological adverse effects? *Diabetes Res Clin Pract*. 88:125–131. 2010.
- Tanaka S, Suzuki K, Aoki C, et al. Add-On Treatment with Teneligliptin Ameliorates Glucose Fluctuations and Improves Glycemic Control Index in Japanese Patients with Type 2 Diabetes on Insulin Therapy. *Diabetes Technology & Therapeutics*. 2014;16(12):840-845. doi:10.1089/dia.2014.0095.
- Tsuchimochi W, Ueno H, Yamashita E, Tsubouchi C, Sakoda H, Nakamura S, et al. Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients. *Endocr J*. 2015;62:13–20.
- Tsuchimochi W, Ueno H, Yamashita E, Tsubouchi C, Sakoda H, Nakamura S, et al. Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients. *Endocr J*. 2015;62(1):13-20.
- Yoshida T, Akahoshi F, Sakashita H, et al. Discovery and preclinical profile of teneligliptin (3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine): a highly potent, selective, long-lasting and orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Bioorg Med Chem*. 2012;20(19):5705–5719.