Original Article

DOI: 10.7860/JCDR/2021/50693.15204

Efficacy and Safety of Linagliptin and Insulin in Patients of Type 2 Diabetes Mellitus with Grade 3-5 Chronic Kidney Disease in a Tertiary Care Hospital

Pharmacology Section

SAAJID HAMEED[1], PANKAJ KUMAR[2], VED PRAKASH[3], MANISH KUMAR[4], HARIHAR DIKSHIT[5]

ABSTRACT

Introduction: Insulin therapy is preferred as safest for glycaemic control in patients with elevated serum urea/creatinine level. Management of diabetes in grade 3-5 Chronic Kidney Disease (CKD) with oral hypoglycaemic is very challenging because most of them cause renal impairment and thus dose adjustment is needed in renal disease. Linagliptin, a DPP-4 (dipeptidyl peptidase-4) inhibitor has only 5% renal excretion; hence its dose adjustment is not needed in patients with CKD.

Aim: To compare the efficacy and safety of linagliptin with insulin in patients of Type 2 Diabetes Mellitus (T2DM) with CKD.

Materials and Methods: The present study was a longitudinal study, in which a total of 101 patients of grade 3-5 CKD with T2DM were divided into two groups, insulin group (n=54) and linagliptin group (n=47), based on their drug therapy. All the cases were tested for HbA1c (Glycated Haemoglobin), Random Blood Sugar (RBS), Creatinine clearance, Urine Protein-Creatinine Ratio (UPCR) and different adverse drug events at their first visit (baseline) and then during follow-up at 1st, 3rd, 6th and 12th month. Statistical analysis was done through GraphPad Instat by unpaired t-test for group comparison and Analysis of Variance (ANOVA) for intragroup comparison.

Results: At the end of study, mean difference of RBS, Creatinine clearance and UPCR in both the groups were not significant. But mean HbA1c level was less in linagliptin group (6.62±0.10) as compared to insulin group (6.82±0.23) on long term therapy and the difference was statistically significant. Hypoglycaemia (33 vs 24), urinary tract infection (6 vs 5) and respiratory tract infection (5 vs 4) were more frequent in insulin group versus linagliptin group.

Conclusion: Linagliptin for glycaemic control provides clinically meaningful improvements in long term glycaemic control without unacceptable side effects in CKD like vulnerable group of patients.

Keywords: Creatinine clearance, Glycaemic control, Glycated haemoglobin, Hypoglycaemia, Urinary tract infection, Urine protein-creatinine ratio

INTRODUCTION

Insulin therapy is preferred as safest for glycaemic control in patient with elevated serum urea/creatinine level. But insulin therapy carries its own drawbacks such as hypoglycaemia, weight gain, lipo-hypertrophy and pain at injection site [1]. Diabetes mellitus is identified as the leading cause of renal impairment which can terminate into End Stage Renal Disease (ESRD) and death [2]. The prevalence of CKD with T2DM is rising worldwide [3,4] and the management of blood sugar level of these patients by oral hypoglycaemic has been challenging. As most of antidiabetic drugs either oral or parenteral can cause renal impairment to some extent hence given at reduced dose [5-7].

Focusing on only managing of CKD and neglecting good glycaemic control can worsen the CKD as standards of diabetes care recommend reducing the risk, or slowing the progression, of CKD by optimising glycaemic control [8]. Patient with T2DM need lifelong therapy hence it should be effective and safe. The drugs should be patient compliant especially in developed countries that have adopted luxurious lifestyles with low physical activity and high intake of energy rich foods [9].

Antidiabetic therapy needs frequent monitoring of blood sugar level due to intrinsic risk of hypoglycaemia. Also, it necessitates regular monitoring of organ functions like renal or hepatic function. These laboratory monitoring build additional economic burden on healthcare delivery systems. DPP-4 inhibitors can solve most of these problems because they are non inferior to sulfonylureas regarding efficacy and there is low risk of hypoglycaemia in their use. They are also body weight neutral and can be given as single dose without any titration. In addition to this, DPP-4 inhibitors have a low rate of adverse events and a good compliance [10].

DPP-4 inhibitors have been perceived as crucial addition to the treatment algorithm in T2DM patients and have been suggested as second-and third-line therapy among other agents within the recent joint position statement of the American Diabetes Association (ADA) and also the European Association for the Study of Diabetes (EASD) [10]. Linagliptin is the first DPP-4 inhibitor available that is mainly eliminated via a hepatobiliary route and only approximately 5% of linagliptin are excreted with the urine in unmetabolised form [11-13]. Therefore, there is no need for a dose adjustment of linagliptin in patients with CKD [14,15].

Various studies have shown significant clinical improvement with linagliptin in T2DM as monotherapy [16-18], in combination with metformin [19], with metformin/sulfonylurea [20], and with thiazolidinedione [21]. Keeping these findings of previous researches in mind and to further strengthen the evidence for the use of linagliptin in higher grades of CKD, this study was planned to compare the efficacy and safety of linagliptin and insulin in patients of T2DM and CKD.

MATERIALS AND METHODS

This was a longitudinal study, conducted at Outpatient Department (OPD) of Endocrinology and Department of Pharmacology at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar, India. This study was approved by Institutional Ethics Committee of IGIMS, Patna (vide Letter No-637/IEC/IGIMS/2018/Dated 18/12/2018). Informed consent was taken from each study participant.

The study duration was from February 2019 to July 2020. In the first six months, 118 study participants were selected (approx. 500 cases of T2DM with 3-5 grade CKD in the hospital [22]. In next months during follow-up, the participant's laboratory parameters were analysed and compared.

Sampling was done keeping 8% margin of error, 95% confidence level and 62% response distribution of diabetes induced CKD.

Inclusion criteria

- Diagnosed cases of T2DM of age above 18 years and of all gender.
- Diagnosed cases of CKD (grade 3-5) [22].

Exclusion criteria

- Patient having previous hypersensitivity reaction to other DPP-4 inhibitors.
- Immunocompromised patients
- Patients having urinary tract or other systemic infections, haematuria, decompensated heart failure, liver failure, debilitating illness that may adversely affect renal function.

Study Procedure

Total of 118 consecutive patients of grade 3-5 CKD with T2DM were selected from OPD of Endocrinology. They were prescribed either insulin or linagliptin as drug therapy. Out of 118 cases, 67 were given insulin therapy and 51 were given linagliptin therapy. In insulin group and linagliptin group data collection of 54 and 47 cases was done because 13 cases from insulin and four cases form linagliptin group didn't turn up during follow-up period.

All the patients were screened for demography and baseline clinical characteristics; and tested for following laboratory tests at their first visit (at baseline) and during follow-up period at 1st month, 3rd months, 6th month and 12th month. The tests were:

- HbA1c (Glycated Haemoglobin)
- RBS (Random Blood Sugar)
- Creatinine Clearance (estimated by the Cockcroft-Gault formula)
- Urine Protein-Creatinine ratio (UPCR)
- Hypoglycaemia and other adverse events

Doses of study drugs were given according to the level of blood sugar of individual patients:

- Insulin-6 units of regular insulin were given before breakfast, before lunch and before dinner in most of the patients with RBS level between 200-300 mg/dL. Single dose of 10 units of insulin glargine was given at bedtime.
- Linagliptin- 5 mg once a day in controlled diabetes. Dose had been increased upto 10 mg when required.

STATISTICAL ANALYSIS

Intergroup comparison was done by unpaired t-test and comparison of parameters in the same group was done by repeated measure ANOVA. Data with p-value <0.05 was considered as statistically significant. GraphPad and MS excel 365 was used for statistical analysis.

RESULTS

The study groups were demographically similar [Table/Fig-1]. Both the groups showed significant improvement in mean RBS and HbA1c. However, decline in mean RBS and HbA1c in linagliptin group was much better than insulin group [Table/Fig-2,3]. There was no significant improvement or decline of mean creatinine clearance seen in either group [Table/Fig-4].

Reduction in mean UPCR was extremely significant in both the groups. At the end of the study, the reduction of mean UPCR in

Variables	Insulin group (n=54)	Linagliptin group (n=47)	p-value (Chi-square)
Age in years (Mean±SD)	60.11±6.35	59.49±6.43	0.62
Sex			
Male (%)	24 (44.44)	21 (44.68)	0.98
Female (%)	30 (55.56)	26 (55.32)	
Duration of diabetes mellitus in years (Mean±SD)	14.78±5.31	14.23±5.83	0.62
CKD Grade (%)			
Grade 3a	9 (16.67)	9 (19.15)	0.99
Grade 3b	28 (51.85)	22 (46.81)	
Grade 4	17 (31.48)	16 (34.04)	
Grade 5	0 (00.00)	0 (00.00)	

[Table/Fig-1]: Demographic and baseline clinical characteristics.

Time	Mean RBS (mg/dL) in insulin Group±SD	Mean RBS (mg/dL) in linagliptin Group±SD	Difference in mean (95% CI)	p-value (Unpaired t-test)
0 month	217.98±13.13	215.00±12.76	2.98 (-2.15 to 8.11)	0.2515 NS
1 months	201.02±13.60	191.98±12.94	9.04 (3.78 to 14.30)	0.0009 S
3 months	186.04±13.90	177.09±13.41	8.95 (3.54 to 14.36)	0.0014 S
6 months	174.07±13.76	169.11±14.04	4.97 (-0.53 to 10.47)	0.0761 NS
12 months	168.07±14.68	163.06±14.82	5.01 (-0.83 to 10.85)	0.0916 NS
p-value between 0 to 12 months (ANOVA)	p<0.00001	p<0.00001		

[Table/Fig-2]: Mean RBS (mg/dL) data at each follow-up.
SD: Standard deviation; CI: Confidence interval; S-Significant; NS: Not significant

Time	Mean HbA1c (%) in insulin Group±SD	Mean HbA1c (%) in linagliptin Group±SD	Difference in mean (95% CI)	p-value (Unpaired t-test)
0 month	8.49±0.45	8.51±0.50	- 0.020 (-0.208 to -0.168)	0.8320 NS
1 months	7.90±0.40	7.61±0.43	0.291 (0.128-0.455)	0.0006 S
3 months	7.41±0.48	7.11±0.24	0.296 (0.143 to 0.449)	0.0002 S
6 months	7.01±0.36	6.81±0.13	0.200 (0.092 to 0.309)	0.0004 S
12 months	6.82±0.23	6.62±0.10	0.201 (0.128 to 0.274)	<0.0001 S
p-value between 0 to 12 months (ANOVA)	p<0.00001	p<0.00001		

[Table/Fig-3]: Mean HbA1c (%) data at each follow-up in two study groups.

Time	Mean creatinine clearance (mL/min) in insulin Group±SD	Mean creatinine clearance (mL/min) in linagliptin Group±SD	Difference in mean (95% CI)	p-value (Unpaired t-test)
0 month	35.83±10.31	36.41±11.88	-0.5800 (-4.9607 to 3.8007)	0.7933 NS
1 months	36.05±10.11	36.53±11.76	-0.4800 (-4.7976 to 3.8376)	0.8259 NS
3 months	35.63±10.23	36.27±11.26	-0.6400 (-4.8836 to 3.6036)	0.7654 NS
6 months	35.11±9.53	36.03±11.67	-0.9200 (-5.1072 to 3.2672)	0.6638 NS
12 months	34.94±9.47	35.38±11.10	-0.4400 (-4.5010 to 3.6210)	0.8302 NS
p-value between 0 to 12 months (ANOVA)	0.9745, NS	0.9902, NS		

[Table/Fig-4]: Mean creatinine clearance (by Cockcroft-Gault Formula in mL/min) (https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc) at each follow-up.

linagliptin group was better than insulin group but the difference was not significant [Table/Fig-5].

The most common adverse event was hypoglycaemia followed by hyperglycaemia in both the groups [Table/Fig-6].

Time	Mean UPCR (mg/mg) in insulin Group±SD	Mean UPCR (mg/mg) in linagliptin Group±SD	Difference in mean (95% CI)	p-value (Unpaired t-test)
0 month	1.19±0.17	1.18±0.19	0.0100 (-0.0611 to 0.0811)	0.7807 NS
1 months	1.07±0.17	1.03±0.13	0.0400 (-0.0205 to 0.1005)	0.1922 NS
3 months	0.93±0.15	0.88±0.15	0.0500 (-0.0094 to 0.1094)	0.0979 NS
6 months	0.81±0.11	0.79±0.12	0.0200 (-0.0254 to 0.0654)	0.3844 NS
12 months	0.75±0.13	0.71±0.11	0.0400 (-0.0079 to 0.0879)	0.1010 NS
p-value between 0 to 12 months (ANOVA)	p<0.00001, S	p<0.00001, S		

[Table/Fig-5]: Mean Urine Protein-Creatinine Ratio (UPCR in mg/mg) at each follow-up.

Adverse events	Insulin group Adverse Event (AE) (%)	Linagliptin group Adverse Event (AE) (%)
Hypoglycaemia	33 (61.11)	24 (51.06)
Hyperglycaemia	17 (31.48)	13 (27.66)
UTI	6 (11.11)	5 (10.64)
Fever	7 (12.96)	6 (12.77)
Respiratory tract infection	5 (9.26)	4 (8.51)
Hyperkalaemia	11 (20.37)	10 (21.28)
Constipation	4 (7.41)	5 (10.64)
Diarrhoea	6 (11.11)	7 (14.89)
Nausea	3 (5.56)	5 (10.64)
Cough	3 (5.56)	2 (4.26)
Pruritus	2 (3.70)	2 (4.26)
Arthralgia	2 (3.70)	3 (6.38)
Back pain	2 (3.70)	4 (8.51)
Abdominal pain	3 (5.56)	3 (6.38)
Dizziness	3 (5.56)	3 (6.38)
Insomnia	2 (3.70)	2 (4.26)
Total	109	98

[Table/Fig-6]: Incidence of adverse drug events.
UTI: Urinary tract infection

DISCUSSION

In this study, the efficacy and safety of linagliptin and insulin was compared in 118 patients of T2DM with grade 3-5 CKD. Linagliptin showed better glycaemic control over insulin on long term therapy. Any deuteriation or reduction of kidney function tests were not evident in either of the groups.

Morton JI et al., found in their study that the cases of ESKD in T2DM patients increases with increasing duration of diabetes and age, suggesting a complex relationship of ESKD risk with age of onset of diabetes [23]. McGill JB et al., conducted a 1-year randomised, double-blind, placebo-controlled study for investigation of the long-term safety, tolerability, and efficacy of an oral hypoglycaemic agent exclusively in patients with T2DM and severe renal impairment, and found that the addition of linagliptin (5 mg once daily) to background insulin therapy provided a clinically significant HbA1c reduction after 12 weeks and this reduction was sustained over 52 weeks [24].

Glycaemic control is most important part of management of diabetic patient [25]. Significant relationship between hyperglycaemia and the development of microvascular complications, such as CKD was demonstrated by several large clinical trials in patients with T2DM [26-28].

However, glucose lowering treatment options are limited in patients with T2DM and CKD because most of the oral anti-diabetic agents are cleared by the kidney. Therefore, in patients with higher grade of CKD, most of these drugs are either not recommended or contraindicated [29].

No significant differences in renal safety parameters between two groups were found in the present study. However, many factors can affect progression of renal disease and longer-term clinical studies are needed to highlight the potential effects of linagliptin on renal function. Along with a previous finding that linagliptin therapy hadn't have any variable effects in patients with normal, mild, or moderate renal impairment [30], the pharmacokinetic data from previous studies also suggest that linagliptin has no potential to accumulate at any degree of renal impairment [24].

In this study, there was a significant decrease in mean UPCR in both the groups. In linagliptin group, mean UPCR decreased from 1.18 at baseline to 0.71 at the end of the study while mean UPCR decrease from 1.19 at baseline to 0.75 at the end of the study. The reduction was more in UPCR in linagliptin group as compared to insulin group. While this difference in UPCR between two group at the end of the study was not statistically significant but this result does highlight need for some more long-term studies.

Some other studies also found that linagliptin therapy can reduce albuminuria which is most important risk factor for progression of CKD and Cardiovascular Disease, therefore producing newer evidences for nephrologists about the therapeutic options for this category of patients [31,32]. Ku E et al., found in their study that there was 8 years lesser time spent in stage 3a, 5.6 years lesser time in stage 3b, but only 6 months lesser time in stage 5 in patients with proteinuria ≥1 g/g as compared to those with proteinuria <1 g/g [33].

Hypoglycaemia was found more frequently in insulin group (61.11 per 100 patients) than linagliptin group (51.06 per 100 patients). Linagliptin is a safe and effective alternative to multi-dose insulin therapy, resulting in similar glucose control with lower hypoglycaemia [34,35].

Limitation(s)

Patients were selected from outdoor unit hence compliance of the patients was not pursued uniformly. The study did not include different drug interactions which might be possible with other medications for CKD. For gathering more refined data about efficacy and safety of linagliptin, studies must be performed on larger populations.

CONCLUSION(S)

This study showed that addition of linagliptin for glycaemic control provides clinically meaningful improvements in glycaemic control without unacceptable side effects in this vulnerable group of patients. This supports the use of linagliptin as an effective, convenient and safe once daily treatment option in patients with T2DM and CKD.

REFERENCES

[1] Powers AC, Alessio DD. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycaemia. Brunton LL, Dandan RH, Knollmann BC. Goodman & Gilman's The Pharmacological Basics of Therapeutics. 13th ed. McGraw Hill Education, New York; 2018: Pp. 873.
[2] Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al. Nephropathy in diabetes. Diabetes Care. 2004;27(Suppl. 1):S79-83.
[3] Grassmann A, Gioberge S, Moeller S, Brown G. ESRD patients in 2004: Global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant. 2005;20:2587-93.
[4] Atkins RC. The epidemiology of chronic kidney disease. Kidney Int Suppl. 2005;94:S14-18.
[5] Powers AC, Alessio DD. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycaemia. Brunton LL, Dandan RH, Knollmann BC. Goodman & Gilman's The Pharmacological Basics of Therapeutics. 13th ed. McGraw Hill Education, New York; 2018: Pp. 882.

[6] Bakris GL. Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. Mayo Clin Proc. 2011;86:444-56.
[7] Shrishrimal K, Hart P, Michota F. Managing diabetes in hemodialysis patients: Observations and recommendations. Cleve Clin J Med. 2009;76:649-55.
[8] American Diabetes Association. Standards of medical care in diabetes 2011. Diabetes Care. 2011;34(Suppl. 1):S11-61
[9] International Diabetes Federation (IDF) (2011) The global burden. In: Diabetes Atlas, 5th ed. Brussels: IDF; Available at: http://www.idf.org/diabetesatlas/5e/the-global-burden.
[10] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577-96.
[11] Powers AC, Alessio DD. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycaemia. Brunton LL, Dandan RH, Knollmann BC. Goodman & Gilman's The Pharmacological Basics of Therapeutics. 13th ed. McGraw Hill Education, New York; 2018: Pp. 863-885.
[12] Blech S, Ludwig-Schwellinger E, Gräfe-Mody EU, Withopf B, Wagner K. The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, in humans. Drug Metab Dispos. 2010;38(4):667-78.
[13] Heise T, Graefe-Mody EU, Hüttner S, Ring A, Trommeshauser D, Dugi KA. Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. Diabetes Obes Metab. 2009;11(8):786-94.
[14] Deacon CF, Holst JJ. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor with an unusual profile for the treatment of type 2 diabetes. Expert Opin Investig Drugs. 2010;19(1):133-40.
[15] Graefe-Mody U, Friedrich C, Port A, Ring A, Retlich S, Heise T, et al. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin. Diabetes Obes Metab. 2011;13(10):939-46.
[16] Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycaemic control and markers of b-cell function in patientswith inadequately controlled type 2 diabetes: A randomised controlled trial. Diabetes Obes Metab. 2011;13:258-67.
[17] Forst T, Uhlig-Laske B, Ring A, Ritzhaupt A, Graefe-Mody U, Dugi KA. The oral DPP-4 inhibitor linagliptin significantly lowers HbA1c after 4 weeks of treatment in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011;13:542-50.
[18] Kawamori R, Inagaki N, Araki E, Watada H, Hayashi N, Horie Y, et al. Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: A randomised, placebo and active comparator-controlled, double-blind study. Diabetes Obes Metab. 2012;14:348-57.
[19] Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: A randomised, doubleblind, placebo-controlled study. Diabetes Obes Metab. 2011;13:65-74.
[20] Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: A 24-week randomised study. Diabet Med. 2011;28:1352-61.
[21] Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: A randomised, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13:653-61.
[22] Dash SC, Agarwal SK, Panigrahi A, Mishra J, Dash D. Diabetes, hypertension and kidney disease combination "DHKD Syndrome" is common in India. J Assoc Physicians India. 2018;66(3):30-33.
[23] Morton JI, Liew D, McDonald SP, Shaw JE, Magliano DJ. The association between age of onset of type 2 diabetes and the long-term risk of end-stage kidney disease: A national registry study. Diabetes Care. 2020;43(8):1788-95.
[24] McGill JB, Sloan L, Newman J, Patel S, Sauce C, Eynatten MV, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment. Diabetes Care. 2013;36(2):237-44.
[25] Afroz A, Ali L, Karim MN, Alramadan MJ, Alam K, Magliano DJ, et al. Glycaemic control for people with type 2 diabetes mellitus in Bangladesh- An urgent need for optimization of management plan. Sci Rep 9, 10248 (2019). https://doi.org/10.1038/s41598-019-46766-9.
[26] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
[27] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53.
[28] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomised prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-17.
[29] Chapelsky MC, Thompson-Culkin K, Miller AK, Sack M, Blum R, Freed MI. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal in-sufficiency. J Clin Pharmacol. 2003;43:252-59.
[30] Friedrich C, Emser A, Woerle HJ, Graefe-Mody U. Renal impairment has no clinically relevant effect on the long-term exposure of linagliptin in patients with type 2 diabetes. Am J Ther. 2013;20(6):618-21.
[31] Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013;36(11):3460-68.
[32] Cooper ME, Perkovic V, McGill JB, Groop PH, Wanner C, Rosenstock J, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. Am J Kidney Dis. 2015;66(3):441-49.
[33] Ku E, Johansen KL, McCulloh CE. Time-centered approach to understanding risk factors for the progression of CKD. CJASN. 2018;13(5):693-701.
[34] Vellanki P, Rasouli N, Baldwin D, Alexanian S, Anzola I, Urrutia M, et al. Linagliptin Inpatient Research Group. Glycaemic efficacy and safety of linagliptin compared to a basal-bolus insulin regimen in patients with type 2 diabetes undergoing non-cardiac surgery: A multicentre randomised clinical trial. Diabetes Obes Metab. 2019;21(4):837-43.
[35] Araki E, Unno Y, Tanaka Y, Sakamoto W, Miyamoto Y. Long-term efficacy and safety of linagliptin in a Japanese population with type 2 diabetes aged ≥60 years treated with basal insulin: A randomised trial. Adv Ther. 2019;36:2697-11.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
2. Junior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
3. Associate Professor and Head, Department of Endocrinology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
4. Associate Professor, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
5. Professor and Head, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Manish Kumar,
Associate Professor, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna-800014, Bihar, India.
E-mail: manu072@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 08, 2021
- Manual Googling: Jun 28, 2021
- iThenticate Software: Jul 09, 2021 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 07, 2021**
Date of Peer Review: **Jun 29, 2021**
Date of Acceptance: **Jun 30, 2021**
Date of Publishing: **Aug 01, 2021**