

Comparison Between Effect of Vildagliptin And Linagliptin on Glycaemic Control, Renal Function, Liver Function And Lipid Profile in Patients of T2DM Inadequately Controlled With Combination of Metformin And Glimepiride.

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Abstract

Objective: Type 2 diabetes mellitus (T2DM) is a progressive disease, pharmacotherapy with a single agent does not generally provide durable glycaemic control over the long time. In this study two dipeptidyl peptidase-4 inhibitors vildagliptin and linagliptin was used for comparative study as add on therapy in type 2 diabetes mellitus patients inadequately controlled with dual combination metformin and glimepiride.

Material And Methods: The study was a prospective, randomized, open label comparison. A total of 234 T2 DM patients who failed to achieve glycaemic control with metformin and glimepiride were recruited to receive vildagliptin or linagliptin as an additional drug. Patients were divided into two groups. One group received vildagliptin and second group received linagliptin as an add on drug with metformin and glimepiride. Fasting and postprandial plasma glucose, glycosylated hemoglobin (HbA1c), lipid profile, liver function, renal function were monitored before and 24 weeks after treatment.

Results: Both the groups were well matched in terms of age, weight, clinical finding and laboratory values. At 24 weeks in both groups, the reduction of blood sugar and glycated hemoglobin were significant and comparable. Effects of linagliptin on renal function and hepatic function was found better than vildagliptin. Significant improvement was observed in low density lipoprotein (LDL-C) levels in patients of linagliptin group.

Conclusion: Both vildagliptin and linagliptin significantly lower blood sugar but linagliptin is better than vildagliptin for renal function, hepatic function and lipid profile

Keywords: Glycated haemoglobin, Dipeptidyl peptidase -4 inhibitors, vildagliptin, linagliptin

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I. Introduction

Type 2 diabetes mellitus (T2DM) affects over 300 million people world wide [1]. The increasing prevalence of diabetes has followed rapid economic growth, increase in life expectancy and life style [2]. Inadequate control of diabetic blood sugar in diabetic patients lead to micro and macrovascular complication [3,4]. The management of diabetes aims at improving glycaemic control to reduce the onset of complications [5]. Glycaemic control is typically measured as reduction in glycosylated hemoglobin (HbA1c). It is 20 years since the idea of inhibiting dipeptidyl peptidase (DPP)-4 was proposed as a potential new therapy for type 2 diabetes [6]. The rationale behind using DPP4 inhibition to treat T2DM is that by inhibiting degradation of the incretin hormone glucagon like peptide-1, its beneficial effect on glucose homeostasis which include both potentiation of glucose induced insulin and suppression of glucagon secretion [7,8] will be enhanced [9]. Dipeptidyl peptidase was first described in 1966 [10] and by the early 1990s, much was known about its kinetic properties and substrate specificity [11]. The DPP-4 inhibitors differ widely in their chemistry and pharmacokinetic properties. Some have longer half-lives such as sitagliptin, linagliptin [12,13,14,15,16], others have much shorter half-lives such as saxagliptin and vildagliptin [17,18]. The different clearance mechanism and substrate specificity influence, to some extent the way in which different DPP-4 inhibitors are used therapeutically [19,20,21,22,23,24]. The present article highlights the different effects of two DPP-4 inhibitors vildagliptin and linagliptin.

II. Material And Methods

Study design- We undertook randomized open label comparative study of type-2 diabetic patients in J.L.N. Medical college & Hospital, Bagalpur between March 2016 to April 2017. Total 234 patients were recruited for the study. Patients were randomly divided into two groups. Group A comprising of 116 patients received vildagliptin (50mg) and group B comprising of 118 patients received Linagliptin (5mg) once daily as add on drugs with metformin (500mg) and glimepiride (2mg). Study procedure- Approval of protocol and study document was taken from institutional ethical committee before study commencement. After taken written informed consent patients were screened for selection criteria

Inclusion criteria-

1. Males and females between age group 40-70 years

2. Patients of type-2 diabetes mellitus

3. Patients having FBG > 126mg/dl and PPBG > 200mg/dl and HbA1c between 7-10%. Exclusion criteria-

1. Males and females patients age < 40 and > 70 years

2. Patients of Type-

1 diabetes mellitus

3.Pregnant and lactating women

4.Patients of acute emergencies like diabetic ketoacidosis, renal failure, liver failure, microvascular complication with history of surgery.

After meeting the inclusion criteria patients were randomized into two groups on the basis of add on drugs to be given . To group A vildagliptin(50mg), metformin (500mg) and glimepiride(2mg) and to group B linagliptin(5mg) , metformin(500mg) and glimepiride (2mg) was given for six months.On the start of the day , day 0, after taking history of the patients and doing clinical examination , routine investigations was sent. The base line FBG, PPBG, HbA1c, lipid profile, eGFR, serum creatinin, SGOT/SGPT were obtained. Patients were followed 15 days regularly. FBG and PPBG were recorded on 15 days interval while HbA1c , lipid profile , SGOT/SGPT , eGFR and serum creatinine level were recorded at the end of study. Statistical Analysis- Values are expressed as the mean± SD. The difference of base line and change in sugar other values between groups were compared using an unpaired t test. The difference between the values before and after the treatment within the same groups were tested using a paired t test. P value < 0.05 considered significant.

III. Results

Table-1 summarizes the base line characteristics of the patients enrolled for this study. There were no significant differences in the background factors between the groups.

| Variables | Vildagliptin(n=116) | Linagliptin(118) |
|----------------------------------|---------------------|--------------------|
| Age | 51.4±13.8 | 50.8±14.9 |
| Gender | 66.5(M) 33.5(F) | 65.4(M) 34.6(F) |
| BMR(kg/cm ²) | 26.49±6.44 | 26.82±4.80 |
| FBG(mg/dl) | 148.6±41.6 | 147.2±32.4 |
| PPG(mg/dl) | 226.4±10.4 | 228.4±10.2 |
| LDL-C(mg/dl) | 130.5±26.6 | 150.2±34.2 |
| HDL-C(mg/dl) | 56.6±10.8 | 56.8±15.1 |
| eGFR(ml/min/1.73m ²) | 101.4±24.6 | 102±34.2 |
| Creatinine(mg/dl) | 0.58±0.2 | 0.62±0.2 |
| AST(IU/L) | 35.2±14.2 | 30.6±19.6 |
| ALT(IU/L) | 46.5±29.5 | 41.8±35.4 |

Values are expressed as Mean±SD(except for gender)

Table-2 Effects of Vildagliptin and Linagliptin after 24 weeks of treatment as add-on drugs

| Variables | Vildagliptin group | Linagliptin group |
|----------------------------------|--------------------|-------------------|
| FBG(mg/dl) | 132.4±20.4 | 128.4±22.2 |
| PPG(mg/dl) | 162.4±10.6 | 160.6±8.2 |
| HbA1c(%) | 6.44±1.19 | 6.84±1.66 |
| LDL-C(mg/dl) | 124±24.4 | 100.4±20.6 |
| HDL-C(mg/dl) | 57±12.2 | 59.2±12.4 |
| eGFR(ml/min/1.73m ²) | 97±26.8 | 103±23.6 |
| Creatinine(mg/dl) | 0.62±0.4 | 0.60±0.3 |
| AST(IU/L) | 34.5±11.8 | 25.4±8.8 |
| ALT(IU/L) | 45.4±20.4 | 38.2±25.4 |

At 24 weeks reduction in blood sugar and HbA1c were significant and comparable in both groups [Table-2 and Figure-1,2]. Renal function was evaluated on the basis of eGFR(ml/min/1.7m²).At 24 weeks eGFR and creatinine were found better in Linagliptin group.[Table-2 and Figure-3). Liver function was evaluated on the basis of aspartate transaminase(AST) and alanine aminotransferase level(ALT).Better improvement were observed in AST and ALT levels in linagliptin group{Table-2}. Lipid profile was evaluated on basis of high density lipoprotein- cholesterol(HDL-C) and low density lipoprotein cholesterol level(LDL-C) which is also better in linagliptin group[Table-2]. Significant improvement were observed in low density lipoprotein cholesterol(LDL-C) level in patients in the linagliptin group[Table-2 and Figure-4].

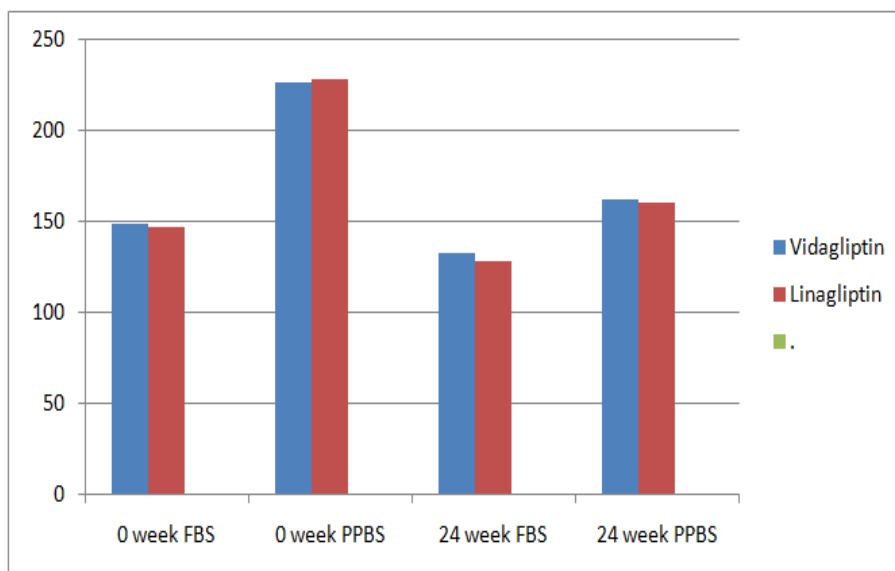


Figure 1. Change in fasting and postprandial blood sugar

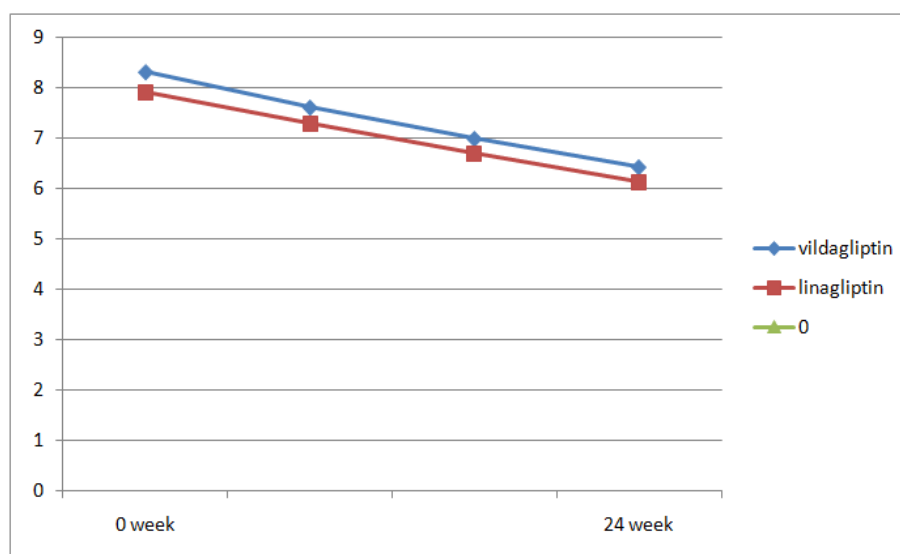


Figure 2. change in HbA1c levels

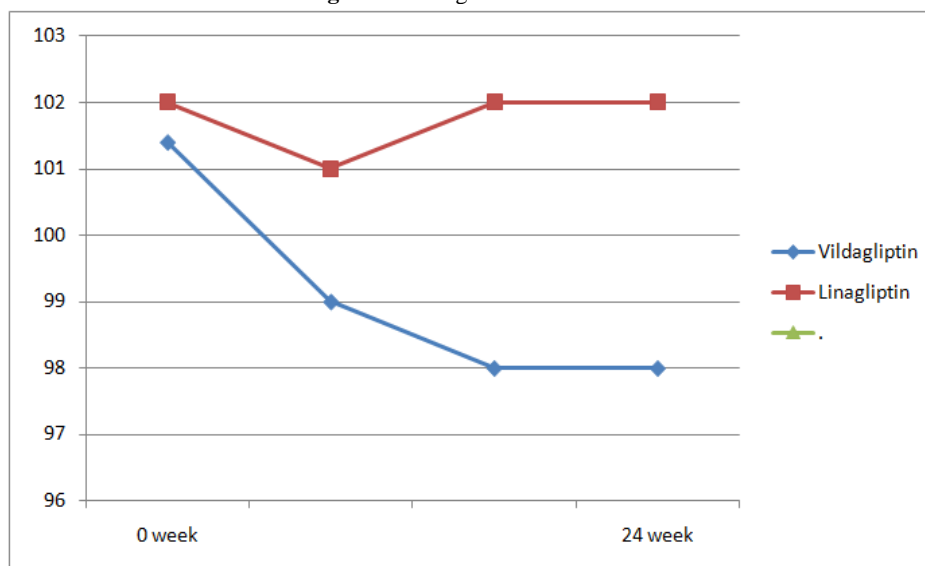


Figure- 3. Change in eGFR

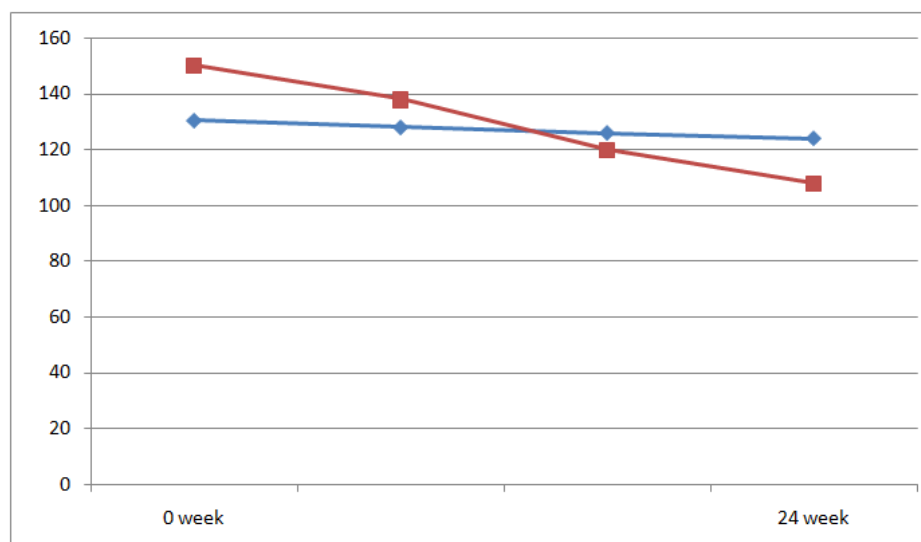


Figure 4. change in ldl-c levels

IV. Discussion

The inability of monotherapy to maintain good glycaemic control in type-2 diabetes mellitus as a result of progressive deterioration of β -cell function provide the rationale for the early use of combination therapy with different classes of drugs . At 24 weeks DPP-4 inhibitors showed excellent effect on the glycaemic control as an add on therapy in treating T₂DM. Our results are in accordance with previous reports[25,26]. Several previous reports demonstrated that DPP-4 inhibitors are efficacious in decreasing HbA1c and enabled patients to reach glycaemic control targets both as monotherapy and combination therapy[27,28].

The DPP-4 inhibitors also differ in their elimination pathways, which can influence their clinical usage. Linagliptin and sitagliptin are not appreciably metabolized, and are eliminated predominantly unchanged. Vildagliptin undergo cytochrome P450(cyp)-independent hydrolysis. Recent data indicate that DPP-4 itself account for 60% of vildagliptin[29,30,31]. The kidneys are important in the final elimination of most of the inhibitors. Compounds such as sitagliptin rely almost exclusively on the kidney for the clearance of the active inhibitor molecules, whereas metabolism is involved for several of other compounds, both parents and metabolite are still predominantly cleared renally. In contrast, the main elimination route for linagliptin is biliary excretion; at its therapeutic dose, linagliptin is mostly protein bound, which minimizes its renal clearance [32,33]. The different clearance mechanism influence , to some extent, the way in which different DPP-4 inhibitors are used therapeutically. All can be used in subjects with renal impairment, but declining renal function will increase exposure to those drugs which are eliminated primarily by the kidney, thus to maintain plasma inhibitor concentration at similar levels to those in subjects with normal renal function require larger dose reduction for alogliptin and sitagliptin than for inhibitors such as saxagliptin and vildagliptin, whose clearance also involve metabolism. For linagliptin, whose clearance is largely independent of the kidney, exposure is unaffected by change in renal function.

V. Conclusion

Both vildagliptin and linagliptin significantly lower blood sugar , their effects on glycaemic control were comparable. Linagliptin is better than vildagliptin for renal function, hepatic function and lipid profile. Significant improvement were observed in low density lipoprotein cholesterol(LDL-C) levels in patients in the linagliptin group.

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