Research Article

A Systematic Review on the Clinical Outcomes of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Context: clinical outcomes of Dipeptidyl Peptidase-4 inhibitors can be beneficial for the patients in controlling high blood sugar it can also cause potential adverse effects **Aim:** The main objective of this study was to assess the risks and benefits of Dipeptidyl peptidase-4inhibitors (DPP-4I) in type 2 diabetes mellitus patients. **Method:** systematical articles on Dipeptidyl peptidase-4 inhibitors were reviewed from the year 2015 up to 2017 from 3 databases such as: EMBASE, COCHRANE and MEDSCAPE and some diabetes associations, the main such were: DPP-4 inhibitor, incretin, type 2 diabetes mellitus, Vildagliptin, Sitagliptin, Linagliptin, Saxagliptin, Alogliptin, 69 citations were included after screening for duplication and biased articles. **Results:** All DPP-4I are efficacious for improving blood glucose level among type 2 diabetes mellitus patients without causing hypoglycemic effects, and they can be used as monotherapy or in combination with other antidiabetic agents, Linagliptin offer uniqueness properties due to its non-renal excretion it improves microalbuminuria, whereas remaining DDP-4I cause a marginal changes on renal function, there is no hepatotoxicity among the DPP-4I no dose adjustment for Linagliptin, Sitagliptin, saxagliptin due non-hepatic excretion, only dose reduction is required for patients with minor hepatic functional impairment taking Vildagliptin and saxagliptin due to their partially elimination via liver,DPP-4I also protect patients for cardiovascular complications due its ability of reducing or maintaining the stability of body weight and lipid profile. They also show a low risk for increasing pancreatitis among T2DM and the others side effect were comparable less when compared to other anti-hyperglycemic agents. **Conclusion:** DPP-4I significantly control blood sugar level by decreasing glycated hemoglobin, fasting blood sugar, random blood sugar and they are not associated with hypoglycemic events they also minimize cardiovascular complications by reducing fats and weight in type 2 diabetes mellitus patients, in addition DPP-4I helps in renal and liver protection. Over all, DPP-4I reduce morbidity and mortality rate among T2DM patients.

Key words: DPP-4I, T2DM, Incretin, Saxagliptin, Linagliptin, Sitagliptin, Vildagliptin, Alogliptin.

INTRODUCTION

Diabetes mellitus is a metabolic disorder occurs when the body does not produce enough insulin or body does not respond to the produced insulin.[1] Early symptoms of DM are frequent urination, increased thirst, hunger, excessive fatigue, loss or gain of weight and slow healing of wound.[2-4] Chronic hyperglycemia is associated with end organ damage, dysfunction, and failure in organs and tissues including the retina, kidney, nerves, heart, and blood vessels.[5] A large number of diabetic patient die from cardiovascular complications such as: stroke, ischemic heart diseases,[6-10] in the last three decades the incidence of diabetes mellitus has boosted from 30 million in 1985 to 425 million in 2018, and it is set to reach 629 million by 2045 When it is not appropriately managed.[11-13] In India, DM is the second highest prevalent disease approximately 1 into 10 in Indian population has DM[14-18] the desired general goals of the treatment of diabetes are to avoid acute metabolic decompensation, prevent or delay the appearance of late disease complications, decrease mortality, and maintain a good quality of life. As for chronic complications of the disease, it is clear that good control of glycemia makes it possible to reduce the incidence of microvascular complications

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(retinopathy, nephropathy, and neuropathy)[19] these can be achieved by keeping blood sugar near to a normal range[20] avoiding hypoglycemia effects[21] and minimizing risk factors such obesity and encouraging physical exercises.[22] The relatively long half-lives of sitagliptin, Linagliptin and Alogliptin facilitate once-daily dosing (Table 1). Saxagliptin is also suitable for once-daily dosing as a result of the presence of the active metabolite, BMS-510849, which inhibits DPP-423. The shorter half-life of vildagliptin requires twice-daily dosing.[23] As vildagliptin and saxagliptin are partially eliminated via the liver, dose reductions are also recommended in patients with hepatic functional impairment.[23-24] The DPP-4 inhibitor act by increasing insulin production, decreasing glycogen production, slow gastric emptying and causing patient to feel satisfaction[21] these oral anti-diabetic agents are more efficacious to control glycated hemoglobin, fasting blood sugar, postprandial blood sugar, blood pressure, fat metabolism and it is very safe for the hypoglycemia effect,[25] Linagliptin offer an extra benefit of nephroprotection due to its biliary excretion.[26] The only drawback of DPP-4 inhibitors have been linked with an increased risk of pancreatitis[27-28] and minor adverse events like GIT problems.[29-30]

METHODOLOGY

Systematically articles were reviewed Dipeptidyl peptidase-4inhibitors 2015-2017. Main search concepts were DPP-4I, incretin, vildagliptin, sitagliptin, linagliptin, saxagliptin, Alogliptin, types 2 diabetes mellitus. Databases such as COCHRANE, EMBASE, and MEDSCAPE were searched and literatures were collected and screened to avoid bias and duplicate for this study. Data also are collected from various associations such as Diabetes and endocrine associations, medical association and their associated sites. In this study 69 citations were reviewed.

RESULTS

Clinical outcomes of dipeptidyl peptidase-4inhibitors are summarized according several studies on various parameters. Sitagliptin was the first selective inhibitor of DPP-4, followed by vildagliptin, saxagliptin, Alogliptin and most recently Linagliptin.[28] (Table 1)

Glycemic Control

DPP-4I show a significant improvement for HbA1c for a weighted mean difference of <0.8% as monotherapy[26,31] Naoto *et al.* in a 24 week follow up in a comparative study between Linagliptin and Sitagliptin involving 42 patients both male and female[26] author concluded that both drugs significantly improve HBA1c, fasting blood sugar and postprandial blood sugar,[32-33] Paul Craddy *et al.* In a meta-analysis comparison study of DPP-4I involving 83 RCTs concluded that there are no major differences between them with regard to improvements in glycemia control.[34] Another study involving a total of 36 double-blind RCTs by M.B. Rehman *et al.* allowing analyses of 54,664 patients author concluded that DPP-4I improve blood sugar and are not associated with risk of hypoglycemic effect in patients with types 2 diabetes mellitus.[35-37]among five DPP-4 inhibitors such as Alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin showed almost similar efficacy in controlling blood glucose in the treatment of type 2 diabetes mellitus, either as monotherapy or in combination therapy.

Renal Function

Drug excretion through kidney may cause declining of renal function due to overexposure, in normal ways the renal function starts to decline with the age, in case of diabetes mellitus patients; diabetic nephropathy which is one of diabetic complications rises and cause mortality and morbidity among them.[38] The outcomes of DPP-4 among diabetic patients on renal function was evaluated on the basis of estimated glomerular filtration rate (eGFR), Creatinine, microalbuminuria, macroalbuminuria data from various studies were checked among these factors microalbuminuria, and creatinine are most widely used in early clinical indicator of diabetic nephropathy[39-40] Among DPP-4I Linagliptin is only excreted by non-renal excretion; in a 24 week study by Naoto Kamatani *et al.* at Toyota Kosei Hospital in Japan eGFR and creatinine was measured to study DPP-4 outcomes on renal for patients taking Linagliptin and sitagliptin[26] and according to the 72 annual meeting of the diabetes Association, both concluded that there was a marginal change on renal function. But due to uniqueness of Linagliptin to be excreted through a non-renal way it is suggested to improve albuminurea.[41,42]

Liver Function

Liver plays an important role in regulating the bodys blood sugar, the buildup of fat in the vital organ makes it harder to control fasting glucose levels. It also makes the body more resistant to insulin, straining the pancreas and its beta cells may aggravate the blood glucose abnormalities. A non-alcoholic fatty liver disease (NAFLD) is strongly associated with insulin resistance and hyperglycemia and it is therefore closely linked to type 2 diabetes mellitus. A gold standard technique for identifying NAFLD is liver biopsy but it is not feasible to perform an invasive and costly procedure in such a large number of population.

In this study effect of DPP-4I on liver function was measured by Alanine aminotransferase (ALT) and alanine amino aspartate (AST) in a comparative study by Naoto Kamatani *et al.* comparing the effect of Sitagliptin and Linagliptin concluded that due to unique property of Linagliptin to be excreted through biliary route; it improve effect of fatty liver[26] other DPP-4I such as vildagliptin and saxagliptin are partially eliminated via the liver, dose reductions are recommended in patients with minor hepatic functional impairment[43-44]Measurement of liver enzymes is recommended within 3 months of beginning of treatment and use of these drug is contraindicated in patients with significant liver disease. With the possible exception of vildagliptin, none of the DPP-4I has shown hepatotoxicity in clinical trials. Vildagliptin has exhibited a low incidence of increased liver enzymes.[45] However, no dosage adjustment of Linagliptin, Alogliptin, saxagliptin, or Sitagliptin is recommended in patients with liver disease.[46]

Lipid Profile

Fats were evaluated on the basis of the high-density lipoprotein-cholesterol (HDL-C) (mg/dl), triglycerides, total cholesterol and low-density lipoprotein-cholesterol (LDL-C) levels (mg/dl). Naoto Kamatani *et al.* in a 24-week comparative study between Linagliptin and sitagliptin both drug have increased HDL to 2.9 mg/dl and 1.2 mg/dl respectively in average.[26] An meta-analysis of placebo controlled trials by valentine vitale *et al.* on the effects on Lipid Profile of Dipeptidyl Peptidase 4 Inhibitors, Pioglitazone, Acarbose, and Sulfonylurea showed that the DPP-4I improve lipids[47] by dropping total cholesterol and triglycerides whereas HDL-C has increased[48-49] Monami M *et al.* conducted a systematic review on meta-analysis of DPP-4 inhibitors and lipids providing data on total cholesterol, high-density lipoprotein, and low-density lipoprotein cholesterol, and triglyceride.[49] Author concluded that the difference in means for endpoint versus baseline total cholesterol in

Table 1 : List of Available DPP-4 Inhibitors with Their Half-Lives

Drug name	Brand available	Dose	FDA approval	Dosage form	Half- life
Sitagliptin	Januvia	25 mg,50 mg,100 mg	2006	tablet	14.4 h
	Istavel	50 mg,100 mg			
	Istamet(sitagliptin+metformin)	50 mg/500 mg,50 mg/1000 mg			
	Janumet(sitagliptin+metformin)	50 mg/500 mg,50 mg,1000 mg			
	Zitamet(sitagliptin+metformin)	50 mg/500 mg			
	Janumet XR CP(sitagliptin+metformin)	100 mg/1000 mg			
Linagliptin	Trajenta	5 mg	2011	tablet	12 h
	Tradjenta	5 mg			
	Ondero	5 mg			
	Trajenta Duo(linagliptin+metformin)	2.5 mg/500 mg,2.5 mg/850 mg,2.5 mg/1000 mg			
Vildagliptin	Galvus	50 mg	2008	tablet	2.8 h
	Zomelis	50 mg			
	Jarla	50 mg			
	Jarla M(Vildagliptin+Metformin)	50 mg/500 mg,50 mg/1000 mg			
	Galvus Met(Vildagliptin+Metformin)	50 mg/500 mg,50 mg/850 mg,50 mg/1000 mg			
	Zomelis Met (Vildagliptin+Metformin)	50 mg/500 mg			
Saxagliptin	Onglyza	2.5 mg, 5 mg	2009	tablet	2.5 h
	Kombiglyze XR(saxagliptin+metformin)	5 mg/500 mg, 5 mg/1000 mg			
Alogliptin	Nesina	25 mg	2010	tablet	21.1 h
	Vipidia	6.25 mg, 12.5 mg, 25 mg			
	Kazano(Alogliptin+metformin)	12.5 mg/500 mg, 12.5 mg/850 mg,12.5 mg/100 mg			
	Vipidomet(Alogliptin+metformin)	12.5 mg/850 mg, 12.5 mg/1000 mg			

patients on DPP-4 inhibitors treatment was significantly higher in comparison with controls. Thus, the DPP-4I offer a beneficial effect on lipid and protection of cardiovascular events.

Weight

Diabetes mellitus is a common prevalent metabolic disorder which is more often associated with obesity in DM patients.[50] Patient's quality of life can be negatively affected by the underlying disease process and its complications many of the available treatment options have adverse effects such as weight gain, hypoglycemia and micro- and macrovascular complications which affect patient's willingness to continue the treatment[51-52] for the management of DM a drug of choice beyond glycemia control it should help in keeping body weight steady or even achieving weight loss and limiting hypoglycemia. Monami M *et al.* in a meta-analysis study from a 41 RCTs on DPP-4I in T2DM for a duration of more than 3months showed a better glucose control and no weight gain when used either as monotherapy or in combination with other agents.[53] Vildagliptin once daily or twice daily as monotherapy or in combination for a 52 week follow-up conducted to evaluate efficacy and tolerability of vildagliptin author concluded that the blood sugar was controlled without weight gain or hypoglycemia[54] in another study by Jothydev *et al.* comparing Sitagliptin (100 mg) with glimepiride (1–3 mg) as add on to insulin, author concluded that sitagliptin has an excellent beneficial effects[55] to achieve a better glycemia control, and significantly it reduces a total daily dose of insulin required, body weight without causing hypoglycemic events.

Cardiac Effects

Cardiovascular is one of macrovascular complications among the diabetes mellitus patients which is the most cause of morbidity and mortality among DM patient.[56-57] In a large study by Scirica BM *et al.* where a total number of 16492 patients with type 2 diabetes who had a history of or were at risk for cardiovascular events were randomly assigned into groups either to receive saxagliptin or placebo and for follow up median of 2.1 years, it concluded that there was no cardiovascular risk or benefit.[58] Another randomized double blinded study of Alogliptin after acute coronary syndrome in patients with type 2 diabetes involving 5380 patients who have either an acute myocardial infarction or unstable angina for a duration of up 40 months (median of 18months) Alogliptin, didn't demonstrable cardiovascular excess in high-risk patients.[59] A meta-analysis by Schweizer *et al.* they pooled the data from 25 phase III vildagliptin trials lasting from 12 weeks to over 2 years, where vildagliptin was used alone or combination with other anti-diabetic agents Patients received either a 50-mg dose of vildagliptin once daily (OD) (n = 1393), twice daily (BID) (n = 6,166) or active and placebo comparators (n=6,061), were used to evaluate Cardiovascular and Cerebrovascular safety of vildagliptin[60] authors concluded that vildagliptin was not associated with an increased risk CCV events in a T2DM population, including among those who are at most risk. In a randomized controlled trial to compare cardiovascular outcome of DPP-4I and glimepiride with 6504 patients in the DPP-4 inhibitors group and 13447 patients in the glimepiride group with placebo control in this study outcome was defined as hospitalization for CVDs, including angina pectoris, myocardial infarction, transient cerebral ischemic attack, heart failure, or cerebrovascular disease or any procedure involving coronary artery bypass grafting or percutaneous coronary intervention author concluded that DPP-4I offer a cardio protective outcome.[61] All of the currently available Dipeptidyl peptidase -4 inhibitors have satisfied safety criteria for the cardiovascular benefits.[62]

Hypoglycemic Effect

Hypoglycemia is one of most common side effect in many anti-hyperglycemia drugs. Various studies were included in other to show the effect of DPP-4I in DM patients. Williams-Herman *et al.* performed a meta-analysis reviewing 19 studies where one group was given sitagliptin and a comparator agent to another group.[63] Sitagliptin 100 mg/day was given either as monotherapy or in combination with other antidiabetic drugs this meta-analysis a total number of 5429 patients received sitagliptin, with 4817 in the comparator group study duration ranged from 12–206 weeks. The author concluded that there was less hypoglycemia in the Sitagliptin group than a comparable group.[53] Rosenstock J, *et al.* in a 52-week follow-up conducted to evaluate efficacy and tolerability of vildagliptin author concluded that vildagliptin control blood sugar without weight gain or hypoglycemia.[54] Many studies were conducted to assess hypoglycemia among DPP-4 in comparison with other anti-diabetic agents have shown improves beta-cell function without weight gain or hypoglycaemia.[63-65]

Gastrointestinal Track

Gastro-intestinal track role start from the ingestion of food, digest food into small particles to be absorbed by the body and undigested food materials are expelled out through anus, ingestion of some drugs and contaminated substances cause GI problems. The incidence of GI due to drugs are common for many drugs. However, Sanjay Karla in his study emerging role of dipeptidyl peptidase

-4inhibitors in management of types 2 diabetes mellitus. Author concluded that the incidence of GI by vildagliptin 50 mg twice daily is comparable to placebo and much less to metformin 2000mg daily around 3 to 4 times incidence of diarrhea, nausea, abdominal pain, dyspepsia and flatulence with metformin than with vildagliptin[66] the adverse events of DPP-4I are ranging from mild to moderate but with a rarely treatment discontinuation of the drugs[67]

Pancreatitis

Pancreatitis is the inflammation of pancreas. The inflammation of pancreas will alter the release of antagonistic hormones produced from pancreas those are insulin and glucagon into the bloodstream and therefore the food metabolism for providing energy will be changed. In this study the clinical outcomes of DPP-4I on pancreas was evaluated from various resources. Ling Li *et al.* in a systemic review and meta-analysis 60 studies (n=353,639), consisting of 55 randomized controlled trials (n=33,350) and five observational studies (three retrospective cohort studies, and two case-control studies; n=320,289) author concluded that the incidence of pancreatitis among patients using incretins is low and that the drugs do not increase the risk of pancreatitis.[28] In a retrospective national wide cohort study conducted using the Taiwan National Health Insurance claim database involving a total number of 8526 Sitagliptin initiators and 8055 acarbose initiators who had hypertriglyceridemia or prior hospitalization history for acute pancreatitis were analyzed for the risk of hospitalization due to acute pancreatitis[68] concluded that use of Sitagliptin was not associated with an increased risk of acute pancreatitis in high-risk diabetic patients with hypertriglyceridemia or with history of acute pancreatitis. Shimin Chen *et al.* on the meta –analysis study on the association between DPP-4I drug s and risk of acute pancreatitis involving 5 case control studies, 5 randomized controlled studies, and 3 cohort studies were selected of the 451 retrieved abstracts the randomized controlled studies and case–control studies have confirmed acute pancreatic whereas the cohort studies didn't confirm the association of DPP-4I with acute pancreatitis.[69]

CONCLUSION

DPP-4I is a good option for reducing blood sugar without causing hypoglycemia effects; it also offers additional benefits by reducing lipid profile, weight, offering renal protection and preventing cardiovascular complications among T2DM patients which is the most cause of death and hospitalization among them. However, the cost of drugs should be a challenge for low income population and life style modification can cause alteration of desired clinical outcomes.

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CONFLICT OF INTEREST

The authors announced that there is no conflict of interest regarding this work of study.

ABBREVIATIONS

eGFR: Estimated glomerular filtration rate; **RTC**: Randomized controlled trial; **DPP-4I:** Dipeptidyl peptidase inhibitor; **T2DM**: Type 2 diabetes mellitus; **NAFLD**: Non-alcoholic fatty liver disease; **ALT**: Alanine amino-transferase; **AST**: Aspartate amino-transferase; **CCV**: Cardio and cerebrovascular; **CVD**: Cardiovascular disease; **OD**: Once daily; **BID**: Twice daily; **GI:** Gastrointestinal

SUMMARY

Dipeptidyl peptidase-4 inhibitors are incretin based therapy which helps in reducing blood sugar glucose in type 2 diabetes mellitus without causing hypoglycemic effect, they also provide great advantages in preventing cardiovascular complications due to their ability to control lipid profile and body weight.

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