World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v6.i6.774

*World J Diabetes* 2015 June 25; 6(6): 774-781
ISSN 1948-9358 (online)


EDITORIAL

# Incretin manipulation in diabetes management

Joseph M Pappachan, AV Raveendran, Rajagopalan Sriraman

Joseph M Pappachan, Department of Endocrinology and Diabetes, New Cross Hospital, the Royal Wolverhampton Hospital NHS Trust, WV10 0QP Wolverhampton, United Kingdom
AV Raveendran, Department of Medicine, Kottayam Medical College, Kerala 686008, India
Rajagopalan Sriraman, Department of Endocrinology, Lincoln County Hospital, LN2 5QY Lincoln, United Kingdom

Author contributions: Pappachan JM and Sriraman R conceived the idea; Pappachan JM and Raveendran AV wrote the initial draft of the paper; all authors contributed to literature search and final preparation of the manuscript.

Conflict-of-interest: Dr. Sriraman R received lecture fees from Astra Zeneca, Novo Nordisk and Novo Nordisk Local Access Advisory Board, and sponsorship from Nono Nordisk to attend international conferences. The other authors have no conflicts of interest to declare.



Correspondence to: Dr. Joseph M Pappachan, MD, MRCP (London), Department of Endocrinology and Diabetes, New Cross Hospital, the Royal Wolverhampton Hospital NHS Trust, Wolverhampton Road, WV10 0QP Wolverhampton, United Kingdom. drpappachan@yahoo.co.in
Telephone: +44-1922-721172
Fax: +44-1922-721172

Received: January 7, 2015
Peer-review started: January 8, 2015
First decision: March 6, 2015
Revised: March 14, 2015
Accepted: April 16, 2015
Article in press: April 20, 2015
Published online: June 25, 2015

## Abstract

Incretin-based therapies have revolutionized the medical management of type 2 diabetes mellitus (T2DM) in the 21st century. Glucagon-like peptide-1 (GLP-1) suppresses appetite and gastric motility, and has trophic effects on pancreas, cardio-protective and renal effects. GLP-1 analogues and dipeptidyl peptidase-4 inhibitors form the incretin-based therapies. Significant reduction of hemoglobin A1c when used as monotherapy and in combination regimens, favorable effects on body weight, and low risk of hypoglycemia are their unique therapeutic benefits. Their safety and tolerability are comparable to other anti-diabetic medications. Concern about elevated risk of pancreatitis has been discarded by two recent meta-analyses. This article discusses the therapeutic manipulation of incretin system for the management of T2DM.

**Key words:** Incretin hormones; Incretin-based therapies; Glucagon-like peptide-1 analogues; Dipeptidyl peptidase-4 inhibitors; Pancreatitis



**Core tip:** Development of multiple pharmaceutical agents by the manipulation of incretin hormone system provided the global scientific fraternity several drugs for the management of type 2 diabetes mellitus (T2DM) in recent years. These agents, the glucagon-like peptide-1 analogues and dipeptidyl peptidase-4 inhibitors, form the incretin-based therapies that benefited T2DM patients with significant reduction of hemoglobin A1c, low risk of hypoglycemia, favorable effects on management of overweight and obesity, and enhanced efficacy in combination regimens for glycemic management with other anti-diabetics. Two recent meta-analyses discarded the concern about elevated pancreatitis risk. The article discusses the incretin-based therapies for the management of T2DM.

Pappachan JM, Raveendran AV, Sriraman R. Incretin manipulation in diabetes management. *World J Diabetes* 2015; 6(6): 774-781 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i6/774.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i6.774

## INTRODUCTION

Incretins are gut hormones secreted in response to meals that modify the biological mechanisms of glucose homeostasis in the body mainly through their effects on the pancreatic endocrine function[1,2]. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two major incretin hormones identified to have major effects on carbohydrate metabolism. Although the concept of incretin effect on glucose homeostasis was introduced as early as 1930s[3], the biological effects of incretins were well-established only in the past 3-4 decades[2]. Approximately 70% of β-cell insulin secretion is controlled by GIP and GLP-1[2]. Native GLP-1 has a very short biological half-life (1-2 min only) being rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) to an inactive molecule that terminates its incretin effect. Research on the biological manipulation of incretin system in animal models in the past few decades showed promising results with development of multiple pharmaceutical agents quite useful in the management of obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome towards the turn of 20$^{th}$ century. This paper discusses an overview of incretin manipulation for the management T2DM.

## BIOLOGICAL EFFECTS OF GLP-1

GLP-1 is a peptide hormone secreted from the entero-endocrine L cells located within the gastrointestinal mucosa (mainly the ileum) that act as nutrient sensors, which release GLP-1 in response to luminal nutrients such as sugars, amino acids, and fatty acids[4]. The secreted GLP-1 binds to the GLP-1 receptors (GLP-1R) distributed widely in various body tissues such as the pancreatic islets, brain, heart, kidney, and the gastrointestinal tract. The binding of GLP-1 to islet cell GLP-1R results in amplification of insulin secretion by the pancreas. This property of augmented insulin secretion in response to gut hormone release related to meal intake is termed as "the incretin effect"[4]. However, the effects of GLP-1R activation in most other tissues still remain elusive.

GLP-1 also has trophic effects on the pancreatic β-cells[4,5]. It has been found to stimulate beta-cell proliferation, enhance the differentiation of progenitor cells in the pancreatic duct epithelium in to new β-cells, and inhibit apoptosis of the β-cells[4]. Fasting and meal-related hyper-secretion of glucagon was demonstrated in patients with T2DM, and GLP-1 was found to be a strong inhibitor of glucagon secretion[4]. The exact mechanism of this effect is unknown. Local increase in insulin levels around the α-cells in response to GLP-1R stimulation and the GLP-1-stimulated somatostatin secretion are thought to be responsible for the inhibition of glucagon secretion[4].

GLP-1 possesses the property of inhibition of gastric motility, gastrin-induced acid secretion in the stomach, and the pancreatic secretion[4,6]. The gastric inhibitory effects of GLP-1 are thought to be mediated through the vagus nerve. GLP-1 also possesses central effects in the brainstem and hypothalamus through which it modulates the appetite, satiety and eating behavior in animals and human beings[4]. GLP-1 also has cardio-protective and renal effects. The physiological aspects of incretin bio-effects are depicted diagrammatically in the Figure 1.

## PHARMACOLOGICAL MANIPULATION OF INCRETIN SYSTEM

Attempts for the pharmacological manipulation of GLP-1 and DPP-4 molecules were areas of immense research interest among the scientific fraternity over the past few 3 to 4 decades that resulted in development of multiple medications, which revolutionized the modern management of T2DM. Through the bio-modulation of GLP-1 molecules to counteract the ultra-short half-life of native GLP-1, a class of drugs termed GLP-1 analogues was invented (also termed as incretin mimetics or inretin analogues). Development of inhibitors of the DPP-4 enzyme resulted in production of multiple drugs that prolong the effects of endogenously synthesized incretin molecules termed as incretin enhancers. These two classes of drugs form the incretin-based therapies which are commonly used in the management of T2DM.

With a significant effect on reduction of hemoglobin A1c (HbA1c), favorable effects on body weight especially in obese T2 diabetic, and a relatively low risk of hypoglycemia[7], these drugs were well accepted by diabetologists and internists in the past few years[1]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently recommended incretin-based therapies as important second line agents for management of T2DM[7,8]. Newer molecules with different therapeutic and pharmacodynamic profiles are being added to this class of drugs.

## GLP-1 ANALOGUES

Native GLP-1 is 30 aminoacid polypeptide hormone that is rapidly degraded by the DPP-4 enzyme. To counteract the ultra-short half-life, alterations in the molecular structure of GLP-1 were attempted resulting in successful invention of a few GLP-1 analogues in

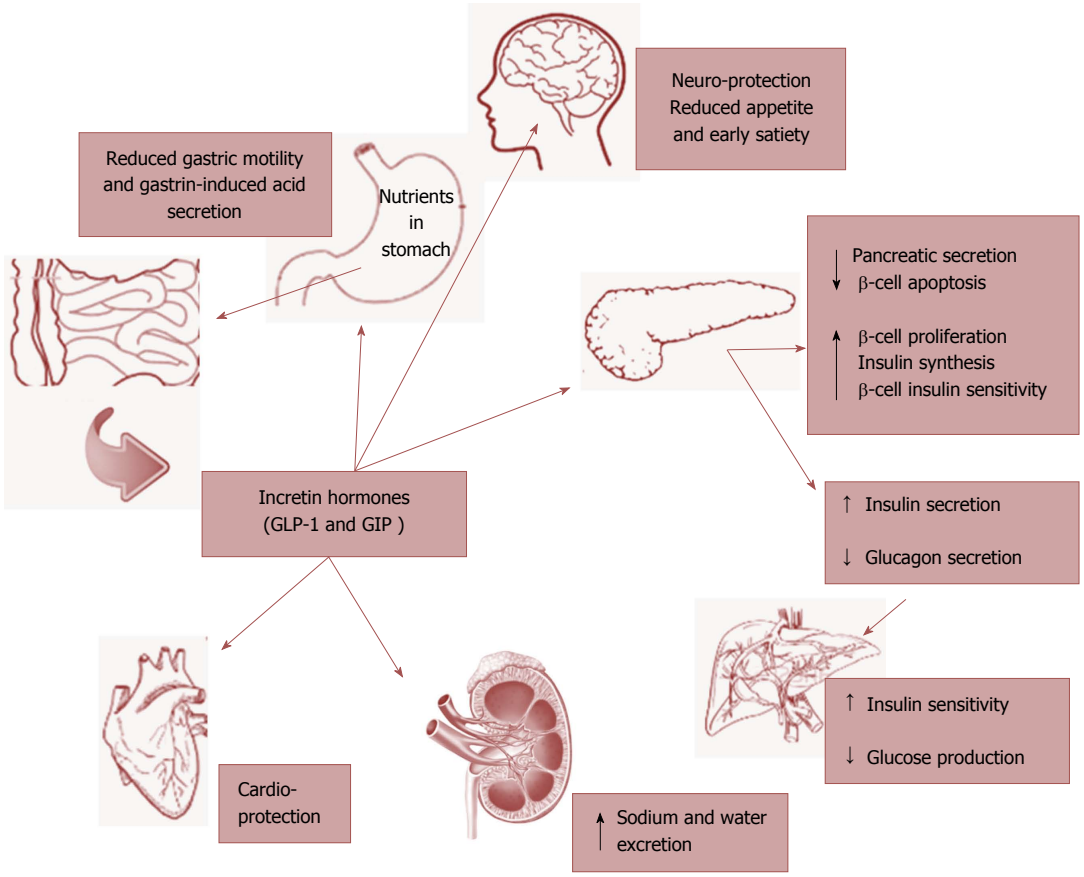


**Figure 1 Physiological aspects of incretin hormones in the body.** GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide.

recent years.

### *Exenatide*

Exenatide is the first among these molecules that gained approval from the United States Food and Drug Administration (FDA) in 2005[9]. The drug, isolated from saliva of the reptile Gila monster (*Heloderma suspectum*), has 39 aminoacids with a 53% structural homology to natural GLP-1[9,10]. It has a plasma half-life of 3-4 h, and is excreted by glomerular filtration with subsequent degradation[10].

Exenatide improved glycemic control in patients with T2DM, not responsive to lifestyle modification, and medications such as sulfonylureas, metformin and thiazolidinediones, either alone or in combinations[9,11]. Exenatide treatment showed improvements in both the fasting and post-prandial hyperglycemia in T2DM patients[12]. In a recent meta-analysis examining the efficacy of the drug compared to placebo from nine clinical trials, the weighted mean difference of mean variation of hemoglobin A1c (Δ HbA1c) for all included data for exenatide 5 μg twice daily or its equivalent long acting dosage form was -0.68% [95%CI: -0.89 to -0.48 ($P$ < 0.0001)] and for exenatide 10 μg twice daily or its equivalent long-acting dosage was -0.99% [95%CI: -1.18 to -0.8 ($P$ < 0.0001)][13]. The weighted mean difference of mean variation of BW (Δ BW) for 5 μg twice daily or its equivalent long acting dosage form in eight of the trials was -0.56 kg [95%CI: -0.07 to -0.06 ($P$ = 0.0002)] and for exenatide 10 μg twice daily or its equivalent long-acting dosage form in twelve trials was -1.24 kg [95%CI: -1.69 to -0.78 ($P$ < 0.0001)]. Other observed benefits were reduction of systolic and diastolic blood pressures, and total cholesterol and low density lipoprotein (LDL)[13].

Being structurally different from native GLP-1, development of antibodies to exenatide on long-term treatment is common. Low-titre anti-exenatide antibodies were observed in 32% of cases on twice daily regimen and in 45% cases on once weekly regimen[14]. However, a significant effect on therapeutic efficacy was not evident in most cases. Higher antibody titres were less common (5% and 12% respectively), and increasing titres were associated with a reduction in average efficacy that was statistically significant for exenatide once weekly preparation[14]. Apart from injection-site reactions, there were no observed safety issues with anti-exenatide antibodies.

### *Liraglutide*

The drug is manufactured using recombinant DNA technology, and is with a 97% structural homology to human GLP-1[15]. Therefore, the molecule can be used effectively in patients with reduced response

to exenatide therapy after prolonged use because of antibody production. The estimated mean differences in HbA1c reduction with liraglutide 1.2 mg and 1.8 mg daily compared to placebo were -1.01% (95%CI: -1.18 to -0.85) and -1.18% (95%CI: -1.32 to -1.04) respectively in a recent meta-analysis[16]. The Liraglutide Effect and Action in Diabetes (LEAD) program trial showed that mono-therapy with 1.2 mg and 1.8 mg of the drug was associated with a mean 2.1 kg and 2.5 kg weight reduction respectively, compared with a mean 1.1 kg weight gain among patients on glimepiride ($P < 0.001$) treatment[17].

The other observed benefits were: a mean reduction in systolic blood pressure of 2.59 mmHg ($P = 0.0008$) and 2.49 mmHg ($P = 0.003$) from baseline for liraglutide 1.2 mg and 1.8 mg respectively at 26 wk of treatment[15], improvement of β-cell function[18], reduction of total cholesterol and LDL, improvement of non-alcoholic fatty liver disease (NAFLD)[19], and improvement of cardiovascular risk markers[15].

### *Lixisenatide*

Plasma half-life of lixisenatide is 3 h similar to that of exenatide[20], although it can be used as a single daily subcutaneous injection. Treatment with the drug resulted in a HbA1c reduction of 0.9%, body weight reduction of -3.62 kg (95%CI: -5.86 to -1.36) without significant risk of hypoglycemia compared to insulin[21]. Lixisenatide was also shown to improve NAFLD (number needed to treat: 14 patients, $P = 0.042$)[22]. Although slightly less effective than exenatide in terms of lowering HbA1c levels and weight reduction, lixisenatide use can be more convenient in comparison to exenatide as it has less hypoglycemia risk and gastrointestinal side effects, and the ease of once-daily administration[23].

### *Albiglutide*

Albiglutide is a DPP4-resistant human GLP-1 manufactured by fusion of the molecule with recombinant human albumin[24]. With a plasma half-life of approximately 5 d, the drug has the advantage of being administered once weekly. The drug recently received FDA approval in the United States for management of T2DM. Albiglutide can be used as a monotherapy or as an add-on therapy to metformin, sulfonylureas, insulin glargine and thiazolidinediones. Superior clinical efficacy compared to sitagliptin, and glimepiride, and non-inferiority to insulins (glargine and lispro) with HbA1c reduction of 0.55% to 0.9% and weight reduction up to 1.21 kg were reported with the use in T2DM cases[25]. Although gastrointestinal side effects were less common, efficacy in reducing HbA1c and body weight were less pronounced compared to liraglutide.

### *Dulaglutide*

This new long acting GLP-1 analogue received recent FDA approval for use in T2DM. The plasma half-life of dulaglutide is approximately 4 d, with a once weekly dosing advantage[26]. Efficacy of once weekly regimen was reported to be superior to: metformin monotherapy, sitagliptin as add-on to metformin, and exenatide as add-on to metformin and pioglitazone, with a safety profile similar to other GLP-1 analogues[27]. The plasma half-lives, dosage range and common side effects of GLP-1 analogues are shown in Table 1.

## DPP-4 INHIBITORS

DPP-4 inhibitors increase the endogenously secreted GLP-1 and GIP concentrations by inhibiting the bio-degradation of these hormones by the DPP-4 enzyme, and thereby enhancing the incretin effect. In patients with T2DM these drugs are effective both as monotherapy and as add-on therapy to sulphonylureas, metformin, thiazolidinediones and insulin. In general, DPP-4 inhibitors are weight neutral, making them favorable options in the management of overweight and obese T2DM patients.

### *Sitagliptin*

Sitagliptin is first among the DPP-4 inhibitors that received FDA approval in 2006. The drug has good oral bio-availability, a half-life of 10-12 h (with once daily dosing advantage), and is eliminated mainly through the kidneys necessitating dose reduction in renal impairment[28]. Sitagliptin improves both fasting and postprandial hyperglycemia in T2DM patients. HbA1c reduction of up to 0.94% has been reported when sitagliptin is used as a monotherapy and better reduction in combination regimens. A recent meta-analysis concluded that sitagliptin had comparable efficacy to metformin in reduction of HbA1c and body weight, and improvement of β-cell function, although inferior to metformin in improvement of insulin sensitivity[29].

### *Vildagliptin*

When used as a monotherapy, this molecule showed glycemic control comparable to sulfonylureas and thiazolidinediones, with the advantages of fewer hypoglycemic episodes and lesser body weight gain[30]. Additional favorable effects on pancreatic alpha- and beta-cell function compared to sulphonylureas were noted with the drug. The plasma half-life of vildagliptin is 1.5-4.5 h and the elimination is mainly through hepatic hydrolysis[28]. HbA1c reduction of 0.5%-1% has been reported with the drug use in T2DM. Use in combination with metformin, further improves glycemic control when metformin monotherapy is insufficient, with good tolerability and safety[30]. Combination regimens with other oral antidiabetic medications and insulins are also effective and well tolerated.

**Table 1 Plasma half-lives, dosage range, average hemoglobin A1c and body weight reduction, and common side effects of glucagon-like peptide-1 analogues**

| Drug | Plasma ½ -life | Dosage | HbA1c reduction | Weight reduction | Adverse effects | Other special features |
|---|---|---|---|---|---|---|
| Exenatide | 3-4 h | 5-10 mcg twice daily s.c, 60 min prior to meal | 0.68%-0.99% | 0.56-1.24 kg | Nausea, diarrhoea, headache, pancreatitis, injection site nodule/reaction, formation of anti-exenatide antibody | Not recommended if Creatinine clearance is < 30 mL/min |
| Exenatide ER | 2 wk | 2 mg s.c once weekly | 0.99% | 1.24 kg | Nausea, diarrhoea, vomiting, pancreatitis, injection site nodule/reaction | Injection at any time independent of meals |
| Liraglutide | 13 h | 0.6-1.8 mg s.c once daily | 1.01%- 1.18% | 2.1-2.5 kg | Nausea, diarrhoea, headache, pancreatitis, injection site reaction, formation of anti-liraglutide antibody and naso-pharyngitis | Store in refrigerator (36-46 $^0$ F) Injection at any time independent of meals |
| Lixisenatide | 3 h | 20 mcg, once daily s.c | 0.90% | 3.62 kg | Nausea, diarrhoea, vomiting, pancreatitis | |
| Albiglutide | 5 d | 30-50 mg s.c once weekly | 0.55%- 0.9% | 1.21 kg | Upper respiratory infection, diarrhoea, injection site reaction, hypersensitivity, pancreatitis | Administer on the same day of the week |
| Dulaglutide | 4 d | 0.75-1.5 mg s.c once weekly | 0.99%- 1.3% | - | Nausea, diarrhoea, vomiting, increased amylase and lipase levels, abdominal pain, injection site reaction, hyper-sensitivity and pancreatitis | |

HbA1c: Hemoglobin A1c.

### *Saxagliptin*

The drug received FDA approval in 2009 for use in patients with T2DM. When used as monotherapy at a maximum dose of 5 mg, saxagliptin caused a mean HbA1c reduction of 0.8% with significant improvement of fasting hyperglycemia, and with other categories of oral anti-diabetics, an additional mean HbA1c reduction by 0.6%-0.7%[31]. The plasma half-life is 2.5 h and elimination is mainly by hepatic and renal clearance[28].

### *Linagliptin*

Linagliptin is primarily excreted *via* bile and therefore safe to be used in T2DM patients with renal impairment. With a reasonable safety profile, low hypoglycemia risk, HbA1c reduction ranging from 0.6% to 0.8% and weight neutrality, the drug became popular in the recent years[32]. Additional benefits such as improvement of wound healing, reduction of hepatic steatosis, decrease in the infarct size following myocardial infarction and ischemic stroke, improvement of vascular function, and reduction of albuminuria are claimed with linagliptin use in pre-clinical studies that needs further research in large randomized controlled trials. Linagliptin has relatively low oral bio-availabilty compared to other DPP-4 molecules (15%-50%) and the plasma half-life of the drug is 12 h[32].

### *Alogliptin*

This new DPP-4 molecule has a plasma half-life of about 21 h, and can be administered once daily[33]. Elimination is mainly through kidneys that necessitates dose reduction in advanced renal disease. Alogliptin is safe and well tolerated. A mean HbA1c reduction of 0.6% is reported with monotherapy[28,33], and additional reduction in combination regimens with other anti-diabetics[33].

### *Teneligliptin*

Teneligliptin is one of the latest additions to the class of DPP-4 inhibitors. A recent study revealed that the drug administration was associated with significant elevations of postprandial active GLP-1 and GIP levels, lowering of postprandial hyperglycemia, 24-h mean blood glucose levels, and mean amplitude of glycemic excursions without hypoglycemia[34]. A significant elevation in early-phase insulin release and a reduction in postprandial glucagon surge were also observed. Even short-term teneligliptin treatment was found to be beneficial in patients with T2DM. HbA1c reduction of about 1%, improvement of β-cell function, insulin sensitivity, and adverse lipid parameters are the benefits claimed in a clinical trial[35].

### *Anagliptin*

The drug is still being evaluated in phase III clinical trials and is expected to be available for clinical use soon. Mean HbA1c reduction of -0.85% ± 0.70%, reduction in the fasting proinsulin/ insulin ratio, and improvement of insulin secretion were observed when used as an add-on therapy to metformin (all effects comparable with sitagliptin) in a recent multi-center clinical trial[36]. Safety profile and efficacy were also comparable with sitagliptin.

The dosage ranges and common side effects of DPP-4 inhibitors are shown in Table 2.

## SAFETY ISSUES/CONCERNS ABOUT INCRETIN-BASED THERAPIES

A lot of discussions on the safety of incretin-based

**Table 2 Plasma half-lives, dosage ranges, average hemoglobin A1c reduction and common side effects of dipeptidyl peptidase-4 inhibitors**

| Drug | Plasma half-life | Dose | HbA1c reduction | Adverse effects | Other remarks |
|---|---|---|---|---|---|
| Sitagliptin | 12.4 h | 100 mg PO daily | 0.94% | Nasopharyngitis, diarrhea, headache, constipation, oedema, hypersensitivity, pancreatitis, elevation of hepatic enzymes | Use with caution in renal, hepatic or cardiac failure |
| Vildagliptin | 90 mts - by terminal elimination | 50-100 mg/ daily PO | 0.5%-1% | Headache, nasopharyngitis, cough, constipation, dizziness, and increased sweating | |
| Saxagliptin | 2.5 h | 2.5-5 mg/PO daily | 0.8% | Urinary and upper respiratory infections, headache, edema, purpuric rash, hypersensitivity, pancreatitis and angio-edema | Dose reduction with CYP450 3A4/5 inhibitors |
| Linagliptin | 12 h | 5 mg PO daily | 0.6%-0.8% | Nasopharyngitis, dyslipidemia, pancreatitis | |
| Teneligliptin | 24.2 h | 20-40 mg PO daily | 0.78% | Constipation, QT interval prolongation, hypoglycaemia and elevation of alanine aminotransferase and γ-glutamyltransferas | |
| Alogliptin | 21 h | 25 mg PO daily | 0.6% | Hypoglycemia, nasopharyngitis, headache and pancreatitis | Monitor LFT and stop if elevated |
| Anagliptin | 4.37 h - by terminal elimination | 100 mg PO daily | 0.85% | Not available | |

HbA1c: Hemoglobin A1c.

therapies occurred recently following multiple case reports and the data from the United States FDA adverse events reporting system about the risk for pancreatic damage[1]. Two recent meta-analyses showed reassuring results without significant risk of pancreatitis favoring incretin-based therapies[37,38]. However, the potential long-term effects of chronic GLP-1R stimulation and its effects on pancreatic enzyme synthesis and the probability of evoking inflammatory response in the pancreas are not clear at the moment.

The other important concern is about the potential to induce neoplasia by these drugs. Significant β-cell hyperplasia, co-expression of insulin and glucagon from β-cells, hyperplasia of α-cells, increased proliferation markers, and excess prevalence of pre-neoplastic lesions were found in pancreas specimens of organ donors previously treated with incretin-based medication for T2DM[39]. Concerns about elevated risk of pancreatic and thyroid cancer in animal models and human beings[40] need further clarification by long-term studies and drug safety monitoring.

## CONCLUSION

Incretin-based therapies are promising tools for the management of T2DM, especially in overweight and obese individuals. Favorable effects on body weight, significant reduction of HbA1c levels and the relatively low risk of hypoglycemia make them attractive therapeutic options in the day to day management of T2DM patients. Newer GLP-1 analogues and DPP-4 inhibitors are being added to this class of medications recently. Concern about elevated risk of pancreatitis is not obvious at the moment, based on results from two large meta-analyses. However, long-term effects of these medications on pancreatitis risk and cancer risk still need vigilant monitoring.

## ACKNOWLEDGMENTS

We are thankful to Blessen P George for his valuable help for the construction of the figure in this article.

## REFERENCES

1 **Pappachan JM**. Incretin-based therapies and pancreatitis risk: myth or reality. *Endocrine* 2015; **48**: 360-362 [PMID: 25433430]
2 **Baggio LL**, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007; **132**: 2131-2157 [PMID: 17498508 DOI: 10.1053/j.gastro.2007.03.054]
3 **Fehmann HC**, Göke R, Göke B. Cell and molecular biology of the incretin hormones glucagon-like peptide-I and glucose-dependent insulin releasing polypeptide. *Endocr Rev* 1995; **16**: 390-410 [PMID: 7671853]
4 **Holst JJ**. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007; **87**: 1409-1439 [PMID: 17928588 DOI: 10.1152/physrev.00034.2006]
5 **Egan JM**, Bulotta A, Hui H, Perfetti R. GLP-1 receptor agonists are growth and differentiation factors for pancreatic islet beta cells. *Diabetes Metab Res Rev* 2003; **19**: 115-123 [PMID: 12673779 DOI: 10.1002/dmrr.357]
6 **Wettergren A**, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 1993; **38**: 665-673 [PMID: 8462365]
7 **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. 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**: 1577-1596 [PMID: 22526604 DOI: 10.1007/s00125-012-2534-0]
8 **American Diabetes Association**. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]
9 **Cho YM**, Wideman RD, Kieffer TJ. Clinical application of

glucagon-like Peptide 1 receptor agonists for the treatment of type 2 diabetes mellitus. *Endocrinol Metab* (Seoul) 2013; **28**: 262-274 [PMID: 24396690 DOI: 10.3803/EnM.2013.28.4.262]

10 **Fineman MS**, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 2003; **26**: 2370-2377 [PMID: 12882864 DOI: 10.2337/diacare.26.8.2370]

11 **Tahrani AA**, Piya MK, Kennedy A, Barnett AH. Glycaemic control in type 2 diabetes: targets and new therapies. *Pharmacol Ther* 2010; **125**: 328-361 [PMID: 19931305 DOI: 10.1016/j.pharmthera.2009.11.001]

12 **Berg JK**, Shenouda SK, Heilmann CR, Gray AL, Holcombe JH. Effects of exenatide twice daily versus sitagliptin on 24-h glucose, glucoregulatory and hormonal measures: a randomized, double-blind, crossover study. *Diabetes Obes Metab* 2011; **13**: 982-989 [PMID: 21615670 DOI: 10.1111/j.1463-1326.2011.01428.x]

13 **Nikfar S**, Abdollahi M, Salari P. The efficacy and tolerability of exenatide in comparison to placebo; a systematic review and meta-analysis of randomized clinical trials. *J Pharm Pharm Sci* 2012; **15**: 1-30 [PMID: 22365085]

14 **Fineman MS**, Mace KF, Diamant M, Darsow T, Cirincione BB, Booker Porter TK, Kinninger LA, Trautmann ME. Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes Metab* 2012; **14**: 546-554 [PMID: 22236356]

15 **Rigato M**, Fadini GP. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes* 2014; **7**: 107-120 [PMID: 24672252 DOI: 10.2147/DMSO.S37644]

16 **Scott DA**, Boye KS, Timlin L, Clark JF, Best JH. A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo. *Diabetes Obes Metab* 2013; **15**: 213-223 [PMID: 22958381 DOI: 10.1111/dom.12007]

17 **Garber A**, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**: 473-481 [PMID: 18819705 DOI: 10.1016/S0140-6736(08)61246-5]

18 **Degn KB**, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 2004; **53**: 1187-1194 [PMID: 15111485 DOI: 10.2337/diabetes.53.5.1187]

19 **Pappachan JM**, Antonio FA, Edavalath M, Mukherjee A. Non-alcoholic fatty liver disease: a diabetologist's perspective. *Endocrine* 2014; **45**: 344-353 [PMID: 24287794 DOI: 10.1007/s12020-013-0087-8]

20 **Christensen M**, Knop FK, Vilsbøll T, Holst JJ. Lixisenatide for type 2 diabetes mellitus. *Expert Opin Investig Drugs* 2011; **20**: 549-557 [PMID: 21391833 DOI: 10.1517/13543784.2011.562191]

21 **Fournier M**, Germe M, Theobald K, Scholz GH, Lehmacher W. Indirect comparison of lixisenatide versus neutral protamine Hagedorn insulin as add-on to metformin and sulphonylurea in patients with type 2 diabetes mellitus. *Ger Med Sci* 2014; **12**: Doc14 [PMID: 25332702 DOI: 10.3205/000199]

22 **Gluud LL**, Knop FK, Vilsbøll T. Effects of lixisenatide on elevated liver transaminases: systematic review with individual patient data meta-analysis of randomised controlled trials on patients with type 2 diabetes. *BMJ Open* 2014; **4**: e005325 [PMID: 25526792 DOI: 10.1136/bmjopen-2014-005325]

23 **Rosenstock J**, Raccah D, Korányi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* 2013; **36**: 2945-2951 [PMID: 23698396 DOI: 10.2337/dc12-2709]

24 **Rosenstock J**, Reusch J, Bush M, Yang F, Stewart M. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care* 2009; **32**: 1880-1886 [PMID: 19592625 DOI: 10.2337/dc09-0366]

25 **Trujillo JM**, Nuffer W. Albiglutide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. *Ann Pharmacother* 2014; **48**: 1494-1501 [PMID: 25136065 DOI: 10.1177/1060028014545807]

26 **Barrington P**, Chien JY, Showalter HD, Schneck K, Cui S, Tibaldi F, Ellis B, Hardy TA. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; **13**: 426-433 [PMID: 21251178 DOI: 10.1111/j.1463-1326.2011.01364.x]

27 **Kuritzky L**, Umpierrez G, Ekoé JM, Mancillas-Adame L, Landó LF. Safety and efficacy of dulaglutide, a once weekly GLP-1 receptor agonist, for the management of type 2 diabetes. *Postgrad Med* 2014; **126**: 60-72 [PMID: 25414935 DOI: 10.3810/pgm.2014.10.2821]

28 **Garg K**, Tripathi CD, Kumar S. Clinical review of sitagliptin: a DPP-4 inhibitor. *J Assoc Physicians India* 2013; **61**: 645-649 [PMID: 24772702]

29 **Du Q**, Wu B, Wang YJ, Yang S, Zhao YY, Liang YY. Comparative effects of sitagliptin and metformin in patients with type 2 diabetes mellitus: a meta-analysis. *Curr Med Res Opin* 2013; **29**: 1487-1494 [PMID: 23927568 DOI: 10.1185/03007995.2013.833090]

30 **Forst T**, Bramlage P. Vildagliptin , a DPP-4 inhibitor for the twice-daily treatment of type 2 diabetes mellitus with or without metformin. *Expert Opin Pharmacother* 2014; **15**: 1299-1313 [PMID: 24837407 DOI: 10.1517/14656566.2014.920009]

31 **Panagoulias GS**, Doupis J. Clinical utility in the treatment of type 2 diabetes with the saxagliptin/metformin fixed combination. *Patient Prefer Adherence* 2014; **8**: 227-236 [PMID: 24627627 DOI: 10.2147/PPA.S34089]

32 **Doupis J**. Linagliptin: from bench to bedside. *Drug Des Devel Ther* 2014; **8**: 431-446 [PMID: 24851042 DOI: 10.2147/DDDT.S59523]

33 **Holland DQ**, Neumiller JJ. Alogliptin in combination with metformin and pioglitazone for the treatment of type 2 diabetes mellitus. *Diabetes Metab Syndr Obes* 2014; **7**: 277-288 [PMID: 25050071 DOI: 10.2147/DMSO.S37648]

34 **Tsuchimochi W**, Ueno H, Yamashita E, Tsubouchi C, Sakoda H, Nakamura S, Nakazato M. Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients. *Endocr J* 2015; **62**: 13-20 [PMID: 25252844 DOI: 10.1507/endocrj.EJ14-0393]

35 **Kutoh E**, Hirate M, Ikeno Y. Teneligliptin as an initial therapy for newly diagnosed, drug naive subjects with type 2 diabetes. *J Clin Med Res* 2014; **6**: 287-294 [PMID: 24883155 DOI: 10.14740/jocmr1841e]

36 **Jin SM**, Park SW, Yoon KH, Min KW, Song KH, Park KS, Park JY, Park IB, Chung CH, Baik SH, Choi SH, Lee HW, Lee IK, Kim DM, Lee MK. Anagliptin and sitagliptin as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, active-controlled, phase III clinical trial with a 28-week extension. *Diabetes Obes Metab* 2015; **17**: 511-515 [PMID: 25523633 DOI: 10.1111/dom.12429]

37 **Li L**, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, Rios LP, Malaga G, Wong E, Sohani Z, Guyatt GH, Sun X. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ* 2014; **348**: g2366 [PMID: 24736555 DOI: 10.1136/bmj.g2366]

38 **Giorda CB**, Sacerdote C, Nada E, Marafetti L, Baldi I, Gnavi R. Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies. *Endocrine* 2015; **48**: 461-471 [PMID: 25146552 DOI: 10.1007/s12020-014-0386-8]

39 **Butler AE**, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas

with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013; **62**: 2595-2604 [PMID: 23524641 DOI: 10.2337/db12-1686]

40 **Elashoff M**, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; **141**: 150-156 [PMID: 21334333 DOI: 10.1053/j.gastro.2011.02.018]

**P- Reviewer**: Georgescu A, Koya D, Schuurman HJ **S- Editor**: Ji FF
**L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com