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Incretin System: Recent Advances in Glucagon Like Peptide-1 and Dipeptidyl Peptidase-4 Inhibitors

Rameshwar Mahaseth

Department of Internal Medicine,
Manmohan Memorial Medical College, Swoyambhu, Kathmandu, Nepal

Correspondence:
Dr. Rameshwar Mahaseth
Department of Internal Medicine,
Manmohan Memorial Medical College & Teaching Hospital (MMTH), Swoyambhu, Kathmandu, Nepal
Email: ramdsh@gmail.com
Phone: 9843076992

Peer Reviewed By
Dr. Buddhi Paudyal
Patan Academy of Health Sciences
Email: buddhipaudyal@pahs.edu.np

Dr. Ashis Shrestha
Patan Academy of Health Sciences
Email: ashisshrestha@pahs.edu.np

ABSTRACT

The endogenous incretins, glucose-dependent insulinotropic polypeptide and Glucagon-like peptide, are peptide hormones secreted from endocrine cells in the small intestine. Glucagon-like peptide-1 stimulates insulin and suppresses glucagon secretion, delays gastric emptying, and reduces appetite and food intake, which explains the positive effect of incretin mimetics on weight. The incretins have also been shown to have a sustained improvement in glycemic control over three years. A wide range of cardiovascular benefits have also been claimed, such as lowering of blood pressure and postprandial lipids. Clinical trials with the incretin mimetic exenatide and liraglutide show reductions in fasting and postprandial glucose concentrations, and haemoglobin A1c (1–2%), associated with weight loss (2–5 kg). The most common adverse event associated with Glucagon-like peptide-1 receptor agonists is nausea, which lessens over time. Orally administered Dipeptidyl Peptidase-4 inhibitors reduce hemoglobin A1c by 0·5–1·0%, with few adverse effects and no weight gain. These new classes of anti-diabetic agents also expand β-cell mass in preclinical studies. However, long-term clinical studies are still needed to determine the benefits of incretin for the treatment of type 2 diabetes.

Keywords: dipeptidyl pedptidase-4 inhibitors, glucagon-like peptide-1 RA, glucose-dependent insulino tropic polypeptide, incretin

INTRODUCTIONS

In the 1960s, data suggested that oral glucose elicited a much greater secretion of insulin than a similar amount of glucose administered intravenously[1] and that this potentiating of insulin secretion by the gut may be responsible for up to 70% of the insulin response to a meal.[2, 3] This physiologic activity was subsequently referred to as the intestinal secretion of insulin, or *incretin* effect. It was later found that two hormones and glucagon-like peptide-1 are responsible for the incretin effect.[3] A key feature of glucagon-like peptide-1 action is the glucose-dependent stimulation of insulin secretion and concomitant suppression of glucagon. Thus, pharmacologic efforts to develop medications that mimic the actions of GLP-1 have become a target for improving or reversing chronic hyperglycemia. Dipeptidyl-like peptidase-4 inhibitors - sitagliptin and vildagliptin are the first agents in this class to have received FDA approval, in addition to saxagliptin and linagliptin.

The Antidiabetic Actions of Incretin Hormones: As knowledge of the pathophysiologic mechanisms of diabetes mellitus has increased, clinical attention has shifted to the incretin system.[6] Hormones secreted from gastrointestinal endocrine cells play key roles in the control of energy balance by regulating the assimilation, storage, and metabolic processing of nutrients.[7] Disruption of these endocrine cells disturbs the normal control of insulin production and body weight, contributing to the development of Diabetes Mellihas Type 2. Two incretin hormones, GLP-1 and GIP, are vital to the control of glucose homeostasis through their ability to increase the β-cell insulin response to ingested glucose.[6,7] These hormones are responsible for more than 90% of the incretin effect observed after glucose ingestion.[6]

GLP-1 and GIP are released within minutes of glucose absorption to increase insulin secretion.[8] GLP-1 is synthesized in L-cells in small bowel and colon, whereas GIP is secreted by K-cells in the duodenum and proximal jejunum. Both GLP-1 and GIP trigger insulin tropic actions by binding to β-cell receptors. GLP-1 receptors are primarily expressed on pancreatic glucagon-containing α, β and δ cells, though they are also widely expressed in the central and peripheral nervous system, lung, heart, and gastrointestinal tract.[8,9] GLP -1 and GIP exert multiple biological effects.[10] The metabolic effects of GLP-1 include: inhibiting glucose-dependent glucagon secretion from α cells; increasing β-cell proliferation and decreasing β-cell apoptosis; slowing gastric emptying; increasing CNS-mediated satiety leading to reduced food intake; indirectly increasing insulin sensitivity and nutrient uptake in skeletal muscles and adipose tissue; and exerting neuroprotective effects.[9,10]

The metabolic effects of GIP include, in addition to increasing insulin secretion, the following: inhibiting gastric acid secretion; bio-regulating fat metabolism in adipocytes; increasing glucagon secretion; increasing β-cell replication; and decreasing β-cell apoptosis.[9,10] Under normal physiologic conditions, fasting plasma glucose (FPG) is managed by tonic insulin and glucagon secretion, but excursions of pat pran dialglucose are controlled by insulin and the incretin hormones.[9] Several key pathologic abnormalities characteristic of T2DM appear to be related to the biologic activities and functions of incretins. Patients with T2DM have impaired incretin function, impaired GLP-1 release, diminished insulinotropic response to GIP, glucoregulatory defects, and impaired glucose homeostasis.[6,9] Table 1 lists the effects of GLP-1 and GIP on defects in glucose metabolism, pancreas function, and energy uptake in patients with T2DM.[11] Importantly, the incretin effect in particular, postprandial production of GLP-1 is impaired in patients with T2DM. The insulin-secretory response, however, can be restored with pharmacologic doses of GLP-1.[12]

Table 1. Action of incretins GLP-1 and glucose dependent insulotrophic polypeptide on pathophysiologic defects in patients with type 2 diabetes mellitus.[11]

Defects in Type 2 Diabetes	Action of Incretins
Impaired glucose stimulated insulin secretion and first phase response	Restoration of glucose dependent insulinotropic effect and lack of postparandial biphasic response
Hypergluccagonemia	Supression of glucagon secretion
Defective hypoglycaemia counter regulation	Glucagon secretion and loss of insulinotropic effect, when plasma glucose is low
Reduced beta cell mass and insulin content	Increased synthesis of proinsulin, possible increased beta cell mass or differentiation of islet precursor cells into beta cells
Accelerated beta cell apoptosis	Possible inhibition of toxin induced beta cell apoptosis
Normal retarded or accelerated gastric emptying	Slowing of gastric emptying
Hypercaloric energy intake, obesity	Supression of appetite/increase satiety, weight loss

Incretin-Based Treatment Options: Glucagon-like peptide-1 is rapidly metabolized by the enzyme DPP-4, resulting in the generation of an inactive compound that makes for a nonviable therapeutic agent.[7] As a result, a number of of GLP-1 homologs (exenatide and lixisenatide) or analogs (liraglutide, dulaglutide, and albiglutide), and inhibitors of DPP-4(sitagliptin, vildagliptin, linaglutin and sexagliptin) have been developed as options for treating patients with T2DM. GLP-1 receptor agonists can produce GLP-1 levels that are more than five times a patient's physiologic levels, and DDP-4 inhibitors result in an approximate two-fold increase in GLP-1 levels.[13]

GLP-1 Receptor Agonists Exenatide (synthetic exendin-4): Its first incretin-related therapy available for patients with type 2 diabetes. It is naturally occurring peptide from the saliva of the Gila monster and has an approximate 50% amino acid homology with GLP-1. It binds to GLP-1 receptors and mimics many properties of GLP-1. GLP-1 is degraded within one to two minutes by DPP-IV within one to two minutes of entering the circulation. But exenatide is resistant to DPP-IV inactivation. Moreover, it is >1000 times more potent than GLP-1 in circulation. It does not stimulate gastric acid secretion or trigger hepatic vagal efferent. Following injection, it is measurably present in plasma for up to 10 hours and therefore suitable for twice a day administration by subcutaneous injection.[14] Exenatide is excreted renally so, it is contraindicated in patients with decreased creatinine clearance (CrCl <30 mL/min) or with end-stage renal disease (ESRD).[17]

Most recently, a multicenter placebo-controlled trial,[15] evaluated the safety and efficacy of twice-daily exenatide in patients whose T2DM was uncontrolled with insulin glargine, with or without oral antihyperglycemic agents. Patients receiving exenatide (n=138) had a mean HbA1c reduction of 1.74%, compared to 1.04 % in patients receiving placebo (n=123) (between-group difference, -0.69; 95% confidence interval (CI), -0.93% to -0.46%; p<.001). Body weight decreased by an average of 1.8 kg with exenatide and increased by an average of 1.0 kg with placebo (between-group difference, -2.7 Kg; 95% CI, -3.7 Kg to -1.7 Kg; p<.001). The incidence of minor hypoglycemia was similar between the two groups. The rates of hypoglycemia observed in patients taking exenatide are largely dependent on the agents with which it is combined. However, patients receiving exenatide experienced higher rates of gastrointestinal adverse effects compared to those receiving placebo.[15]

Two clinical studies[18,19] of exenatide (5 µg or 10 µg once daily) demonstrated mean increases in the homeostasis model assessment–β-cell (HOMA-B) index, a commonly used measure of β-cell function, of 19% at 24 weeks and 32% at 30 weeks. In patients with T2DM, exenatide normalizes the loss of first-phase insulin secretion and glucagon hypersecretion from β cells, thereby reducing hepatic glucose production in the postprandial state.[16] Guidelines from both the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) have recommended using exenatide and liraglutide as third-line agents in obese (body mass index (BMI) >30 kg/m^2) patients who do not meet glycaemic targets on a combination of metformin and a sulphonylurea.

Long Acting Exenatide: Preliminary experience with exenatide LAR in 45 patients with type 2 diabetes indicates a much greater reduction in fasting glucose concentrations and HbA1c after once weekly administrations of exenatide LAR for 15 weeks compared with exenatide twice daily.[24] A recent study comparing 2 mg preparation of exenatide –LAR given once weekly with conventional exenatide 10 mcg given twice daily showed a greater reduction in HbA1c levels with exenatide –LAR and highly effective with once weekly injection. However, nausea has been reported less frequently with once weekly than with twice daily administration (26% versus 50%).[25]

Liraglutide: Liraglutide is a GLP-1analogue with 97% sequence identity to the human hormone. Liraglutide contains a single amino acid substitution relative to endogenous GLP-1 and is linked to a fatty acid chain, resulting in slow absorption into circulation, increased reversible albumin binding, and reduced susceptibility to DPP-4. These effects extend liraglutide's benefits, increasing its plasma half-life to 11 to 15 hours.[20,21] with maximal concentration after eight to twelve hours.[22] Injected once daily, at any time of day, irrespective of meals, liraglutide reduced fasting blood glucose and glycemic excursions associated with all meals.[14]

In LEAD-1, LEAD-2, and LEAD-4, researchers tested the use of liraglutide combined with glimepiride, metformin, or metformin and rosiglitazone, respectively. These combination regimens reduced mean HbA^{1c} levels by more than 1% over 26 weeks.[27-29] In LEAD-5, once-daily liraglutide was compared directly with insulin glargine in patients receiving concomitant metformin and glimepiride.[30] Liraglutide led to significantly lower HbA^{1c} levels compared with glargine (p=.0015). As is commonly observed following transition to insulin,[31] patients starting glargine gained weight. Convercsely, those administered liraglutide lost weight, with a difference of 3.5 kg at study's end.[30] The final LEAD study, LEAD-6, offers a head-to-head comparison between the two GLP-1 receptor agonists.[32] In this study, liraglutide and exenatide both significantly reduced HbA^{1c} levels relative to baseline. However, the extent of this reduction was significantly greater for liraglutide (p<0.0001). Treatment-associated nausea declined with time for both study arms but persisted longer in patients treated with exenatide. Analysis across the available LEAD studies shows a consistent improvement in HbA^{1c} levels with liraglutide (1.0% to 1.6%), and a very low incidence of hypoglycemic episodes. In addition, liraglutide treatment was associated with sustained weight loss, systolic blood pressure reduction, and improved β-cell function.[29,30, 32]

There have been reports suggesting that both treatments with exenatide,[33] and liraglutide,[34] the most common GLP-1 receptor agonists, are associated with an increased risk of pancreatitis. As chronic pancreatitis is also a known risk factor for pancreatic cancer through cytotoxicity

of inflammatory cytokines, reactive oxygen species, and proliferation,[35] there might be an increased risk of pancreatic cancer as well. It has also been observed in preclinical studies that incidence of thyroid C- cell tumors was increased in rodents treated with GLP-1 analogs.[36] Therefore, monitoring f or thyroid cancer has been a focus in the clinical development plans of all DPP-4 inhibitors and GLP-1 receptor agonists, but thus far the data have been reassuring.

Taspoglutide: Another extended release molecule works on a once weekly basis promising results in phase 2 studies. Tapsoglutide has a 93% homology to endogenous GLP-1. The development of tapsoglutide was recently discontinued because of hypersensitivity concerns, an effect that has not been seen with any of the other approved or experimental GLP-1 mimetics.

Albiglutide: It is a human GLP-1 receptor agonists with two molecules of GLP-1 linked to albumin. The half life is about five days making once weekly dosing possible. In phase 2 trials, HbA1c reduction observed after 16 weeks were similar for dosages 30 mg weekly, 50 mg bi-weekly and 100 mg monthly.

DPP4 Inhibitors: Oral DPP4 inhibitors increase the availability of endogenous GLP-1, thus enhancing glucose-induced insulin secretion and inhibiting glucagon release. These agents have no effect on gastric emptying,[38, 39] and do not affect body weight.[37]

Sitagliptin and Vildagliptin: Sitagliptin and vildagliptin are the first agents in this class to have received FDA approval. Sitagliptin is potent, highly selective, reversible and competitive inhibitor of DPP-4 enzyme and exerts its anti-hyperglycemic effect by slowing the inactivation of incretin hormones. Sitagliptin has been associated with an approximate two-fold increase in postprandial GLP-1 plasma concentrations, compared to placebo in healthy human study participants and in patients with T2DM.[40,41] A comprehensive meta-analysis of trials of once-daily sitagliptin (available in Canada and elsewhere) or twice-daily vildagliptin (marketed in Europe) concluded that these agents were well tolerated,[42] although infections including nasopharyngitis, upper respiratory tract infections, and urinary tract infections, were significantly increased with sitagliptin (relative risk 1.15 compared with placebo 95% confidence interval 1.02 to 1.31;p=.03). They are indicated as monotherapy and in combination with metformin, thiazolidinedione (TZD) and insulin. Headache was reported for both drugs but was more common in patients taking vildagliptin.[42]

Because sitagliptin is cleared by the kidneys, dosage adjustments are recommended in patients with moderate to severe renal insufficiency and in patients undergoing dialysis. For patients with moderate renal insufficiency (Crcl 30-50 ml/min), the sitagliptin dose should be reduced to 50 mg. For patients with severe renal insufficiency (Crcl <30 ml/min) or end-stage renal disease, a sitagliptin dose reduction to 25 mg is indicated.[44] Vildagliptin is not recommended for use in moderate renal failure.

Saxagliptin: Saxagliptin is another DPP-4 inhibitor approved by FDA for the treatment of patients with T2DM.[45] It is a potent, reversible, competitive agent that selectively inhibits DPP-4.[46] As with sitagliptin, saxagliptin exerts its glucoregulatory actions through prevention of incretin degradation, leading to potentiation of GLP-1 and GIP action.[46] The efficacy of saxagliptin has been studied as monotherapy and in combination with metformin, sulfonylureas, and TZDs. During 24 to 102 weeks of treatment with saxagliptin, glycemic efficacy has been demonstrated in patients with T2DM regardless of age, gender, race/ethnicity, or body weight.[46] When used as monotherapy, saxagliptin 5 mg once daily produced mean HbA1c reductions of 0.5% to 0.7%.[46,47] When used in combination with traditional oral hyperglycemic agents, saxagliptin 5 mg once daily (as add-on therapy or as initial combination therapy) provided clinically important reductions in HbA1c level.[46] Saxagliptin, when used with metformin, produced mean reductions in HbA1c levels of 0.7% to 2.5%,[53,54] when used with a sulfonylurea, HbA1c mean reduction was 0.6% 60; and when used with a TZD, HbA1c mean reduction was 0.9%.[48]

The usual dose of saxagliptin is 2.5 or 5 mg once daily, with 2.5 mg dose recommended for patients with moderate to severe kidney disease (CrCl <50 mL/min) and for patients taking strong CYP3A4/5 inhibitors, such as ketoconazole.[46] The most common adverse events observed with saxagliptin are similar to those of sitagliptin, such as headache, nasopharyngitis, upper respiratory tract infections, and urinary tract infections.[46]

Linagliptin: In May 2011, linagliptin became the latest DPP-4 inhibitor to be approved by the FDA for the treatment of patients with T2DM.[49] Similar to sitagliptin and saxagliptin, linagliptin is a potent, highly selective, DPP-4 inhibitor.[50] In approximately 4000 patients with T2DM in clinical trials, linagliptin as monotherapy or in combination with other oral antihyperglycemic drugs was generally well tolerated, with a low incidence of hypoglycemia.[50] The usual dose of linagliptin is 5 mg once daily. No dose adjustment is needed in patients with renal or hepatic impairment. Inducers of CYP3A4 (eg Rifampin) may decrease the efficacy of linagliptin. Therefore, patients requiring such drugs should receive an alternative to linagliptin.

Table 2. Comparison of DPP-4 and GLP-1 RAs.[52]

Effects/parameters	DPP-4 inhibitors	GLP-1 receptor agonists
Route of administration	Oral	Subcutaneous injection
Dose/timing of administration	Once daily	Once or twice daily or once weekly
A1c reduction	0.5%-1.0%	0.6-1.9%
Body weight	Neutral	Reduced
Hypoglycemic	Low incidence	Low incidence
Insulin secretion	Enhanced	Enhanced
Post prandial hyperglycemia	Reduced	Reduced
Glucagon secretion	Suppressed	Suppressed
Appetite	No effect	Suppressed
Gastric emptying	No effect	Slowed (Short acting agent)
Gastrointestinal	None	Nausea, diarrhea, vomiting

GLP-1Receptor Agonists versus DPP-4 Inhibitors: Various similarities and differences exist between GLP-1 receptor agonists and DPP-4 inhibitors.[51,52] Among the differences between these two drug classes, GLP-1 receptor agonists are administered via subcutaneous injection, while DPP-4 inhibitors are delivered as oral tablets. Glucagon-like peptide-1 receptor agonists are probably more effective than DPP-4 inhibitors at reducing HbA1c levels (Table2).[52] Glucagon-like peptide-1 receptor agonists help preserve β cells, which are diminished with DPP-4 inhibitors; induce weight loss, unlike DPP-4 inhibitors; and have beneficial effects on blood pressure that, have not been demonstrated with DPP-4 inhibitors.[51,52]

FUTURE DEVELOPMENTS

Many new incretin-based agents are under investigation for the treatment of patients with T2DM. Albiglutide, exenatide LAR, and lixisenatide are investigational GLP-1 receptor agonists in late stages of clinical development.[55] Liraglutide and exenatide are first-generation GLP-1 receptor agonists, requiring once or twice daily parenteral administration, respectively. Much effort continues to be directed towards improvement of the pharmacokinetic profile of GLP-1R agonists, to minimize peak levels of the drug and thus reduce the extent of nausea. Longer-acting GLP-1R agonists should ideally provide more uniform and sustained GLP-1R activation over a 24-h period, but require less frequent administration.

CONCLUSIONS

The treatment of patients with T2DM remains complex and challenging for physicians. Because GLP-1 receptor agonists work in a glucose-dependent manner, they are likely to reduce hyperglycemia safely, without a marked fluctuation toward hypoglycemia. In the process of acutely restoring β-cell function, GLP-1 agonists may allow patients to achieve HbA^{1c} <7%, without experiencing weight gain or hypoglycemia. These incretin-based medications demonstrate improved efficacy and safety relative to traditional agents, and they represent a major paradigm shift in the treatment of patients with diabetes mellitus and might be considered as first-line therapy after metformin, and insulin therapy (mainly long-acting analogs) could be added if A1C is not at target, mainly when fasting or pre-prandial glucose levels are high. The safety of constant DPP-4 or GLP-1therapy over time is not yet fully clear. Presently, the benefits of using DPP-4 inhibitors or GLP-1 receptor agonists for treatment of type 2 diabetes outweigh the risks. Nonetheless, their safety profile should be monitored and their indications should be widened cautiously.

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REFERENCES

1. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967 Dec;46(12):1954-62.
2. Nauck MA, Busing M, Orskov C, Siegel EG, Talartschik J, et al. Preserved incretin effect in type 1 diabetic patients with end-stage nephropathy treated by combined heterotopic pancreas and kidney transplantation. Acta Diabetol. 1993;30:39–45.
3. Holst JJ, Vilsboll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297:127–36.
4. Langley AK, Suffoletta TJ, Jennings HR. Dipep-tidyl peptidase IV inhibitors and the incretin system in type 2 diabetes mellitus. Pharmacotherapy. 2007;27(6):1163-80.
5. Pinkney J, Fox T, Ranganath L. Selecting GLP-1agonists in the management of type 2 diabetes: dif-ferential pharmacology and the therapeutic benefits of liraglutide and exenatide. Ther Clin Risk Manag. 2010;6:401-11.
6. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696-705.
7. Freeman JS. Role of the incretin pathway in the pathogenesis of type 2 diabetes. Cleve Clin J Med. 2009;76(suppl 5):S12-S19.

8. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-57.
9. Khoo J, Rayner CK, Jones KL, Horowitz M. Incretin-based therapies: new treatments for type 2 diabetes in the new millennium. Ther Clin Risk Manag. 2009;5(3):683-98.
10. Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. Pharmacotherapy. 2010;30(6):609-24.
11. Fonseca VA, Zinman B, Nauck MA, Goldfine AB, Plutzky J. Confronting the type 2 diabetes epidemic: the emerging role of incretin-based therapies. Am J Med. 2010;123(7):S2-S10.
12. Paul ES, Lawrence AL, Subodh V. The incretin system and cardiometabolic disease. Can J Cardiol. Feb 2010;26(2):87–95.
13. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice -daily exenatide in Basal insulin –treated patients with type 2 diabetes: a randomized, controlled. Ann Intern Med. 2011;154(2):103-12.
14. Neumiller JJ. Differential chemistry (structure), mechanism of action, and pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. J Am Pharm Assoc. 2009;49(suppl 1):S16-S29.
15. Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. Pharmacotherapy. 2010;30(6):609-24.
16. Zinman B, Hoogwerf BJ, Duran Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2007;146(7):477-85.
17. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2008;30(8):1448-60.
18. Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, Pedersen FZ, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. J Med Chem. 2000;43(9):1664-9.
19. Degn KB, Juhl CB, Sturis J, Brock B, Chandramouli V, Rungby J, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and α- and β-cell function and reduces endogenous glucose release in patients with type 2 diabetes. Diabetes. 2004;53(5):1187-94.
20. Elbrønd B, Jakobsen G, Larsen S, Agersø H, Jensen LB, Rolan P, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. Diabetes Care. 2002;25(8):1398-404.
21. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373(9662):473-81.
22. Kim D, MacConnell L, Zhuang D, et al. Safety and efficacy of a once-weekly, long-acting release formulation of exenatide over 15 weeks in patients with type 2 diabetes. Diabetes. 2006;55(suppl 1):116.
23. Chakraborti CK. Exenatide: A new promising antidiabetic agent. Indian J Pharm Sci. 2010 Jan-Feb;72(1):1–11.
24. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374:39–47.
25. Marre M, Shaw J, Brandel M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26(3):268-78.
26. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 Study. Diabetes Care. 2009;32(1):84-90.
27. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met+TZD). Diabetes Care. 2009;32(7):1224-30.
28. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52(10):2046-55.
29. Davies M, Lavalle-Gonzalez F, Storms F, Gomis R. Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the AT.LANTUS trial. Diabetes Obes Metab. 2008;10(5):387-99.
30. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. 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(9662):473-81.
31. Denker PS, Dimarco PE. Exenatide (exendin -4)-in duced pancrea titis: a case report. Diabetes Care. 2006;29:471.
32. Buse JB , Rosenstock J, Sesti G, et al . LEAD -6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26 -week randomised, parallel -group, multi-national, open -label trial (LEAD -6). Lancet. 2009;374:39–47.
33. Rebours V, Boutron -Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut. 2009;58:97–103.
34. Bjerre Knudsen L, Madsen LW, Andersen S, et al. GLP- 1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151:1473–86.

35. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008;(2):CD006739.
36. Ahrén B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. Diabetes Care 2007;30(6):1344-50.
37. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes. 1998;47(11):1663-70.
38. Freeman JS. Role of the incretin pathway in the pathogenesis of type 2 diabetes. Cleve Clin J Med. 2009;76(suppl 5):S12-S19.
39. Herman GA, Stevens C, Van Dyck K, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther. 2005;78(6):675-88.
40. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4(DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008;(2):CD006739.
41. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011;141:150–6.
42. Gallwitz B. The evolving place of incretin-based therapies in type 2 diabetes. Pediatr Nephrol. 2010;25(7):1207-17.
43. Onglyza (saxagliptin) tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2009. http:// packageinserts.bms.com/pi/pi_onglyza.pdf. Accessed March 15, 2011.
44. Kulasa K, Edelman S. Saxagliptin: the evidence for its place in the treatment of type 2 diabetes mel-litus. Core Evid. 2010;5:23-37.
45. Rosenstock J, Aquilar-Salinas C, Klein E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin. 2009;25(10):2401-11.
46. Hollander P, Li J, Allen E, Chen R. Saxagliptin added to a thiazolidine-dione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone . J Clin Endocrinol Metab. 2009;94(12):4810-9.
47. Tradjenta (linagliptin) tablets [prescribing infor-mation]. Ridgefield, CT: Boehringer Ingelheim; 2011. http: // hcp. trad jenta. com /prescribing information.jsp. Accessed May 18, 2011.
48. Scott LJ. Linagliptin in type 2 diabetes mellitus. Drugs. 2011;71(5):611-24.
49. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. Diabetes Care. 2010;33(2):428-33.
50. Macconell L, Pencek R, Li Y, Maggs D, Porter L. Exenatide once weekly: sustained improvement in gly- ycemic control and cardiometabolic measures through 3 years. Diabetes Metab Syndr Obes. 2013;6:31–41.
51. Nauck M, Frid A, Hermansen K, et al. LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009;32(1):84-90.
52. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R, et al. Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009;11(6):611-22.
53. De Fronzo RA, Hissa M, Garber AJ, et al. Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes on metformin alone. Diabetes Care. 2009;32(9):1649-55.
54. Search for clinical trials. US National Institutes of Health ClinicalTrials.gov Web site. http://clinical trials.gov/. Accessed July 1, 2011.
55. Ban K, Hui S, Drucker DJ , Husain M. Cardiovascular consequences of drugs used for the treatment of diabetes: potential promise of incretin-based therapies. J Am Soc Hypertens. 2009;3:245–59.
56. Reid T. Diabetes. 2012;(30)1: 3-12; scheen AJ. Eur J Int Med. 2012;23(2):126-131; Rosenstok J, et al: Int J Clin Pract Suppl. 2008;(159):15-23.