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**Special Features:** Incretin-based therapies in type 2 diabetes mellitus

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**CONTEXT:** Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretins secreted from enteroendocrine cells post-prandially in part to regulate glucose homeostasis. Dysregulation of these hormones is evident in T2DM.

Two new drug classes, exenatide (GLP-1 mimetic) and sitagliptin (dipeptidyl peptidase [DPP] 4 inhibitor) have been approved by regulatory agencies for treating T2DM. Liraglutide (GLP-1 mimetic) and vildagliptin (DPP 4 inhibitor) are expected to arrive on the market soon.

**EVIDENCE ACQUISITION:** The background of incretin-based therapy and selected clinical trials of these four drugs are reviewed. A MEDLINE search was conducted for published articles using the key words incretin, GIP, GLP-1, exendin-4, exenatide, DPP 4, liraglutide, sitagliptin, and vildagliptin.

**EVIDENCE SYNTHESIS:** Exenatide and liraglutide are injection-based. Three-year follow-up data on exenatide showed a sustained weight loss and HbA<sub>1c</sub> reduction of 1%. Nausea and vomiting are common. Results from phase 3 studies are pending on liraglutide. Sitagliptin and vildagliptin are orally active. In 26-week studies, sitagliptin educes HbA<sub>1c</sub> by 0.6-0.8% as monotherapy, by 1.8% as initial combination therapy with metformin, and by 0.7% as add-on therapy to metformin. Vildagliptin monotherapy lowered HbA<sub>1c</sub> by 1.0-1.4% after 24 weeks. Their major side effects are urinary tract and nasopharyngeal infections and headaches. Exenatide and liraglutide cause weight loss while sitagliptin and vildagliptin do not.

**CONCLUSION:** The availability of GLP-1 mimetics and DPP 4 inhibitors has increased our armamentarium for treating T2DM. Unresolved issues such as the effects of GLP-1 mimetics and DPP 4 inhibitors on  $\beta$  cell mass, the mechanism by which GLP-1 mimetics lowers glucagon

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levels, and exactly how DPP 4 inhibitors lead to a decline in plasma glucose levels without an increase in insulin secretion, need further research.

## OVERVIEW

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed “incretins”, are enteroendocrine hormones released into the bloodstream from L- and K-cells dispersed throughout the gastrointestinal tract in response to ingested nutrients. They provide the additional stimulus to insulin secretion during oral glucose ingestion which is not present with intravenous (IV) glucose infusion (1, 2). These incretins increase insulin secretion in a glucose-dependent manner through activation of their specific receptors on  $\beta$  cells.

In newly diagnosed type 2 diabetes mellitus (T2DM) with relatively good glycemic control ( $HbA_{1c}$ ~6.9%), both GIP and GLP-1 secretion in response to glucose and mixed meal challenges are the same or even increased when compared to healthy subjects (3, 4). However, in long standing T2DM with poor glycemic control ( $HbA_{1c}$ ~8-9%), the GLP-1 response is decreased while GIP secretion is unchanged (5-7). In addition, insulin response to exogenous GLP-1 is three- to five-folds lower in T2DM. However, acute GLP-1 administration is able to increase insulin secretion to normal levels and to effectively lower plasma glucose (8, 9). In contrast, exogenous GIP, even at supraphysiological doses, has markedly reduced insulinotropic actions with little or no glucose-lowering effects in T2DM (9, 10). Therefore, therapeutic strategies for T2DM within the incretin field focused on the use of GLP-1, GLP-1 analogs and GLP-1 receptor (GLP-1R) agonists or GLP-1 mimetics, and not GIP.

GLP-1, when administered at pharmacologic doses, also has other non-insulinotropic effects beneficial for treating T2DM: suppression of glucagon secretion in the presence of hyperglycemia and euglycemia but not hypoglycemia leading to improved hepatic insulin

resistance and glycemic control (11, 12); slowing of gastric emptying and gut motility causing delayed nutrients absorption and dampened post-prandial glucose (PPG) excursion (13); increase the duration of postprandial satiety leading to lower food intake, weight loss and improved insulin resistance (14-16). More importantly, acute GLP-1 infusion normalized fasting plasma glucose (FPG) in patients with long-standing, uncontrolled T2DM who were no longer responsive to sulfonylureas or metformin (17).

One major drawback of GLP-1 treatment is its short half-life (2 minutes) (18). GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP 4) which cleaves the N-terminal dipeptides (His<sup>7</sup>-Ala<sup>8</sup>) from GLP-1 (7-36) and renders the resulting major metabolite GLP-1 (9-36) inactive (Figure 1) (19, 20). In addition, neutral endopeptidase (NEP) 24.11 hydrolyzes GLP-1 at six different places (21). With short half-life, bolus subcutaneous (SC) injections resulted in only a transient effect on insulin secretion and plasma glucose levels (22).

Nonetheless, in patients with T2DM, bolus SC administration of GLP-1 before breakfast, lunch and dinner for seven days significantly improved PPG and decreased plasma lipid levels (23). Overnight IV GLP-1 infusions lowered FPG and PPG to near-normal levels, markedly improved  $\beta$  cell function and restored first-phase insulin secretion, absence of which is a hallmark of T2DM (24).

Continuous SC GLP-1 infusion via a pump for 6 to 12 weeks improved glucose-induced insulin secretion, enhanced insulin-mediated glucose disposal, and increased insulin pulse mass and pulsatile insulin secretion in T2DM (25, 26). Six weeks of GLP-1 infusion also restored first-

phase insulin secretion in T2DM hence demonstrating the insulintropic potency of long-term GLP-1 treatment (15).

Recent animal studies suggest that exogenous GLP-1 has the ability to increase islet size, enhance  $\beta$  cell proliferation, inhibit  $\beta$  cell apoptosis, and regulate islet growth (27, 28). These effects have tremendous implication in the treatment of T2DM as they directly address one of the fundamental defects in T2DM, that is,  $\beta$  cell failure.

Collectively, the above studies demonstrated the potential of using GLP-1-based therapy for treating T2DM. Two options for GLP-1-based therapies are GLP-1 mimetics resistant to DPP 4 activity hence a longer half-life, and agents such as DPP 4 inhibitors which increase plasma endogenous GLP-1 levels. In this review we will focus on: (1) exenatide (GLP-1 mimetic) and sitagliptin (DPP 4 inhibitor) that have been approved by regulatory agencies for treatment of T2DM as well as liraglutide (GLP-1 mimetic) and vildagliptin (DPP 4 inhibitor) that are expected to arrive on the market soon; and (2) on issues that are still open for debate regarding the actions of these agents.

## GLP-1 MIMETICS

Given that DPP 4 cleaves peptides with an alanine, proline, or hydroxyproline in the penultimate N-terminal position, various modifications of GLP-1 at His<sup>7</sup>, Ala<sup>8</sup>, or Glu<sup>9</sup> have been investigated (29). Additional mid-chain modifications of GLP-1 to prevent NEP hydrolysis are also being investigated to provide longer plasma half-life. Exenatide and liraglutide are two compounds that exhibit these characteristics.

### ***EXENATIDE***

Exenatide (synthetic exendin-4) is the only GLP-1R agonist approved by regulatory agencies as an adjunct therapy to patients with T2DM not achieving satisfactory glycemic control. It is a 39-amino acid peptide produced in the salivary glands of Gila monster (*Heloderma suspectum*) with 53% amino acid homology to full-length GLP-1. It binds more avidly to GLP-1R than GLP-1 in GLP-1R-expressing cells (30). There appears to be no specific exendin-4 receptor. Exendin-4 is not a substrate for DPP 4 because it has a Gly<sup>8</sup> in place of an Ala<sup>8</sup> (Figure 1). In addition, it lacks some of the target bonds for NEP and its secondary and tertiary structures may also prevent NEP hydrolysis. Exenatide, being a peptide, must be injected subcutaneously, and is eliminated by the kidneys through glomerular filtration (31). It has a mean half-life of 3.3 to 4 hours, is detected in the plasma 15 hours after SC injection, and has biological effect 8 hours after dosing (32).

*Selected Clinical Studies:* Clinical trials investigating exenatide as adjuvant therapy to patients with T2DM not achieving adequate glycemic control on metformin and/or sulfonylurea, metformin and/or thiazolidinedione, as well as comparison trials with insulin glargine and

biphasic insulin aspart, are summarized in Table 1 (33-39). With exenatide 10µg twice-daily as adjuvant therapy to oral hypoglycemic agents, significant number of patients (32-62%) achieved  $HbA_{1c} \leq 7\%$  when compared to placebo (7-13%), glargine (48%), and biphasic insulin aspart (24%), and  $HbA_{1c}$  reductions of 0.8-1.1% were sustained up to 3 years,. Progressive weight loss from 1.6-2.8 kg noted at 30 weeks to 5.3 kg at 3 years was also noted. Anti-exenatide antibodies were detected in 41-49% of patients in the treatment arms but were not associated with glyceimic control (33-38).

Side Effects: A meta-analysis on the randomized controlled trials with exenatide showed that severe hypoglycemia was rare. Mild to moderate hypoglycemia was 16% versus 7% (exenatide versus placebo) and more common with co-administration with a sulfonylurea. The most common side effects of exenatide were nausea (57%) and vomiting (17%). Nausea was usually mild to moderate in nature and being most common during the initial 8 weeks of therapy and declined thereafter. Overall, 4% of patients withdrew from the studies because of gastrointestinal side effects (40).

### ***LIRAGLUTIDE***

Liraglutide is a long-acting GLP-1 analog with a substitution of Lys<sup>34</sup> with Arg<sup>34</sup>, and an attachment of a C-16 free-fatty acid derivative via a glutamoyl spacer to Lys<sup>26</sup> (Figure 1). The free-fatty acid derivative is thought to promote non-covalent binding of liraglutide to albumin; therefore, increasing plasma half-life through protection from renal clearance and slow absorption rate from injection site (41). Like GLP-1 and exenatide, liraglutide needs to be injected subcutaneously. After subcutaneous injection, maximum plasma concentrations is reached after 10-14 hours and it has a half-life of 11-13 hours (42, 43).

*Selected clinical trials:* In a 5-week dose-escalation study, liraglutide/metformin combination was associated with a 0.8% reduction in HbA<sub>1c</sub>, a 70 mg/dL reduction in fasting glucose when compared to metformin alone. In addition, liraglutide/metformin significantly reduced fasting glucose (21.6 mg/dL) and body weight (2.9 kg) when compared to metformin/glimepiride group; and liraglutide/placebo significantly reduced fasting glucose (25.2 mg/dL) when compared to metformin/placebo group (Table 1)(44). In a 14-week study of liraglutide versus placebo, liraglutide significantly reduced HbA<sub>1c</sub> by 1.45%, 1.40%, and 0.98% in the 1.90, 1.25, and 0.65 mg groups respectively, while placebo group had an increase of 0.29% in HbA<sub>1c</sub>. The percentages of patients achieved HbA<sub>1c</sub> ≤ 7% were 46%, 48%, 38%, and 5% in the 1.9, 1.25, 0.65 mg groups and the placebo group, respectively (Table 1)(45). The results from Phase 3 trials have not been presented at scientific meetings or published in peer-reviewed journals.

*Side effects:* Most frequently report adverse events were nausea and vomiting especially at the higher doses (40, 45). There is also no development of antibodies noted in trials up to 14 weeks (45-47).

***UNRESOLVED ISSUES REGARDING GLP-1 AND GLP-1 MIMETICS***

***1. Does GLP-1 and GLP-1 mimetics have favorable effects on  $\beta$  cell mass in humans?***

Studies have shown that exenatide has favorable effects on parameters of  $\beta$  cell function in humans using indirect measures such as first-phase insulin secretion and Homeostasis Model Assessment (HOMA)  $\beta$  cell index (48, 49). In rodent studies, GLP-1 induced glucose sensitivity in glucose-resistant  $\beta$  cells (50). Exenatide given to rodents in pharmacological doses, appeared to have beneficial effects on  $\beta$  cell mass not seen with other anti-diabetic agents. However, whether exenatide has a favorable effect on  $\beta$  cell mass *in humans* is unknown.

Exenatide prevented cytotoxic agent-induced apoptosis of rodent islets (51), and chronic treatment increased  $\beta$  cell turnover in rodents (52). GLP-1 also inhibited non-chemically induced  $\beta$  cell apoptosis in freshly isolated human islets (53). Both decreased apoptosis and increased  $\beta$  cell turnover should and do lead to increases islet size and  $\beta$  cell numbers. The trophic effects of exenatide on  $\beta$  cells in rodents are seen with concentrations not achieved in clinical practice. While markers of  $\beta$  cell function show improvement in humans with chronic exenatide use of up to three years (39), this improvement in function may be due to the restoration of glucose-competence to  $\beta$  cells and the insulinotropic, glucose-lowering, and weight-loss effects of exenatide, and *not* because of any direct effect of exenatide on  $\beta$  cell mass.

***2. What is the mechanism by which GLP-1 and GLP-1 mimetics lower glucagon secretion from  $\alpha$  cells?***

Elevated fasting and post-prandial plasma glucagon levels throughout the day is a feature of T2DM (54), and Exenatide treatment lowers both (55). The ability for exenatide and GLP-1 to lower glucagon levels in patients with T2DM most likely contributes to its overall glucose-lowering effect. Additionally, by virtue of enhancing endogenous insulin secretion concurrently with suppressing glucagon secretion, a more physiologic insulin-to-glucagon ratio in the portal vein should be established resulting in better suppression of hepatic glucose output. Whether GLP-1 and GLP-1 mimetics lower glucagon secretion from  $\alpha$  cells through direct or indirect mechanisms is still unclear.

The presence of GLP-1R on human  $\alpha$  cells has not been directly investigated. Overnight IV GLP-1 administration to fasted T1DM subjects resulted in lowering of plasma glucagon levels that was postulated to be a direct effect of GLP-1 on  $\alpha$  cells (56). However, given that plasma C-peptide levels were doubled by GLP-1 infusion, an indirect action mediated by the stimulatory effect of GLP-1 on residual neighboring  $\beta$  (or  $\delta$ ) cells resulting in intraislet paracrine inhibition of glucagon release is also plausible, though at considerably lower insulin concentrations than in healthy or T2DM subjects. A transgenic model of  $\beta$  cell dysfunction also favors a paracrine effect of GLP-1 on glucagon secretion. Mice with a  $\beta$  cell-specific mutation of the *pdx-1* gene had defective insulin secretory and glucagon suppressive responses to exenatide, both of which were present in wild-type mice (57). This strongly suggests that a  $\beta$  cell secreted factor is absolutely necessary for GLP-1-mediated suppression of glucagon secretion.

Rodent data on the presence or absence of GLP-1R on  $\alpha$  cells is not convincing either way. Neither GLP-1Rs nor their transcripts could be detected in purified rat  $\alpha$  cells (58, 59). Direct GLP-1 application to rat  $\alpha$  cells did not alter glucagon secretion or cause an increase in cAMP levels (58, 59). However, GLP-1R expression was detected by immunocytochemistry in a subpopulation (20%) of glucagon-positive cells in dispersed rat islets (60). Since this is a small number of cells and the cells were not obtained with precise methodology, such as laser-captured microscopy, contaminating cells may be the source of the GLP-1R expression.

Furthermore, GLP-1 was also recently reported to elicit an increase in the cAMP content and glucagon secretion in an  $\alpha$  cell line transfected with the GLP-1Rs (61). Therefore, if  $\alpha$  cells actually contain GLP-1Rs, increased glucagon secretion would be the expected response to elevated plasma GLP-1 levels or exenatide therapy. Finally, neuronal control of glucagon secretion through the autonomic nervous system is well recognized and this pathway may be mediated by GLP-1. Therefore GLP-1 and exenatide infusion may cause glucagon suppression *in vivo* via feedback from vagal afferents where neuronal networks are intact but not *in vitro* from dispersed  $\alpha$  cells or cell lines. Regardless, the mechanism underlying suppressed plasma glucagon levels by exenatide is an interesting area of research and may offer insights as to how glucagon secretion might be controlled in T2DM.

## **DPP 4 INHIBITORS**

If pharmacological levels of exogenous GLP-1 can lower blood glucose in T2DM, it is logical to assume that supra-physiological levels of *endogenous* active GLP-1 (aGLP-1) can also lower blood glucose. No secretagogue of L cells has been specifically developed, though clear headway has been made in elucidating how food products bring about GLP-1 secretion from L cell (Figure 2) (62-64). Compared to wild-type mice, DPP knockout mice have elevated fasting incretin levels, lower plasma glucose, and higher plasma insulin levels after a glucose challenge. (65). There has been immense interest at disrupting DPP 4 activity in humans to increase plasma aGLP-1 levels. Sitagliptin and vildagliptin are two such DPP 4 inhibitors.

### ***SITAGLIPTIN***

Sitagliptin, an organic molecule, appears to be selective for DPP 4 and not interact with other closely related proteases (Figure 1) (66). Sitagliptin is rapidly absorbed, achieving peak plasma levels 1-6 hours post-dosing. Its half-life is 8-14 hours with bioavailability of 87%, with or without food (67, 68). About 80% of the dose is excreted unchanged by the kidney with 15% of the bioavailable drug metabolized by CYP3A4 and CYP2C8 in the liver (67, 69). At 100 mg daily, greater than 80% of plasma DPP 4 activity is inhibited over a 24 hour period (67, 70). A dose reduction to 50 mg is needed if creatinine clearance (CrCl) is <50 mL/min and to 25 mg if CrCl is < 30 mL/min (71).

*Selected clinical studies:* Five 24-week trials in T2DM patients examined sitagliptin monotherapy; comparison of sitagliptin monotherapy, metformin monotherapy, and initial combination therapy of sitagliptin and metformin; sitagliptin added to ongoing pioglitazone; sitagliptin added to ongoing metformin; and sitagliptin added to ongoing sulfonylurea and/or

metformin (Table 1) (72-76). As initial therapy, sitagliptin/metformin combination therapy worked better than either sitagliptin or metformin monotherapy with HbA<sub>1c</sub> reduction of 1.9% as compared to 0.6-0.7% and 1.13% after 24 weeks. As adjuvant therapy, sitagliptin in combination with metformin, glipizide, or pioglitazone yielded an HbA<sub>1c</sub> reduction of 0.6-0.7% when compared to placebo.

Preliminary results from 30-week extension trials on sitagliptin monotherapy, initial sitagliptin combination therapy with or without metformin, and sitagliptin as adjuvant therapy to metformin showed that the reduction in HbA<sub>1c</sub> was sustained at week 54 (77-79). A 52-week trial on sitagliptin versus glipizide as adjuvant therapy to metformin showed a reduction in HbA<sub>1c</sub> of 0.7% in both groups, however, the maximal HbA<sub>1c</sub> reduction was observed at 24-30 weeks with a gradual rise in HbA<sub>1c</sub> from week 30-52, which raises the issue of declining sitagliptin efficacy (80). Sitagliptin is reported to be weight neutral. Currently, there is an ongoing study on adding sitagliptin to exogenous insulin in patients with or without metformin treatment (81).

Side effects: Pooled analysis of 5141 patients in clinical trials for  $\leq 2$  years showed that sitagliptin monotherapy or combination therapy (metformin, pioglitazone, sulfonylurea, or sulfonylurea and metformin) was well tolerated and hypoglycemia occurred in the setting of combination therapy (82). The adverse events that were higher with sitagliptin compared to non-exposed groups included nasopharyngitis, contact dermatitis, osteoarthritis (82). A systematic review and meta-analysis of incretin therapies showed that sitagliptin has no risk of gastrointestinal adverse events but has an increase risk for urinary track infection, headache, and especially nasopharyngitis (40) and may reflect a lack of DPP 4 activity required for immunosurveillance.

## ***VILDAGLIPTIN***

Vildagliptin, a selective, reversible, and competitive inhibitor of DPP 4, is a low molecular weight compound suitable for oral dosing (83, 84). Post-dosing, vildagliptin is rapidly absorbed and achieving peak plasma levels in 1-2 hours. Its half-life of 2 hours is shorter than sitagliptin (85, 86). Its bioavailability is 85 % (87), and its pharmacokinetics is not affected by food (88). At 100 mg daily, it inhibits 98% of DPP 4 activities 45 min after dosing and 60% at 24 hours. Although 85% of vildagliptin is ultimately excreted by the kidney and its hydrolysis to LAY151, an inactive metabolite, remains the main metabolic pathway and accounts for 69% of total elimination from the body. A study suggested that there was no significant difference in exposure to vildagliptin in patients with various degrees of hepatic impairment (89). In 2007, the FDA has requested additional data on patients with renal impairment before granting final approval of vildagliptin (90).

*Selected clinical trials:* Six clinical trials evaluated vildagliptin as initial monotherapy in comparison to placebo, metformin, rosiglitazone or acarbose, and also as initial combination therapy with pioglitazone in comparison to vildagliptin monotherapy in drug-naïve patients with T2DM patients (Table 1) (91-97). Patients with worse glycemic control (HbA<sub>1c</sub> ~8.4% versus 6.7%) had bigger HbA<sub>1c</sub> reduction over 24 weeks. Data from the extension study on the group with better glycemic control showed that maximum HbA<sub>1c</sub> reduction occurred around 24-30 weeks followed by gradual rise thereafter until week 108.(92). As monotherapy, vildagliptin 50 mg twice-daily was as effective as rosiglitazone 8 mg once-daily and acarbose 100 mg trice-daily in lowering HbA<sub>1c</sub> but not as effective as metformin 1000 mg twice-daily (94, 95, 97). Initial

combination therapy with vildagliptin and pioglitazone provided better glycemic control than either vildagliptin or pioglitazone monotherapy (96).

Vildagliptin is effective as adjuvant therapy when administered to patients inadequately controlled with sulfonylurea, metformin, thiazolidinedione, or insulin therapy with HbA<sub>1c</sub> reduction of 0.6%, 0.9%, 1.0%, and 0.5% respectively (98-101). In addition, vildagliptin and pioglitazone were equally effective as adjuvant therapy for patients with inadequate controlled on metformin where HbA<sub>1c</sub> reduction of 0.9% and 1.0% were noted, respectively(102).

*Side effects:*

The side effects from vildagliptin are comparable to that of sitagliptin. In a systematic review and meta-analysis of incretin therapies, vildagliptin has no risk of gastrointestinal adverse events but has an increase risk for urinary track infection, and headache (40).

## ***UNRESOLVED ISSUES REGARDING DPP 4 INHIBITORS***

### ***1. Do DPP 4 inhibitors have favorable effects on $\beta$ cell mass in humans?***

Exenatide appears to have beneficial effects on  $\beta$  cell mass when given in pharmacological doses to rodents (51, 52). The effect of DPP 4 inhibitors on  $\beta$  cell mass is less clear. Three-month treatment of high-fat-fed diet streptozotocin-induced diabetic mice with des-fluoro-sitagliptin was reported to preserve  $\beta$  cells from apoptosis with no increase in  $\beta$  cell mass (103).  $\beta$  cells of DPP 4 knock-out mice are also reported to be more resistant to the toxic effects of streptozotocin (104). But against DPP4 inhibitors being trophic factors, 8-week treatment with vildagliptin had no obvious effects on  $\beta$  cell turnover or  $\beta$  cell mass in mice (105).

### ***2. Is the modest increase in aGLP-1 levels the sole modulator of glycemia using DPP 4 inhibitors?***

DPP 4 inhibitors were developed to augment biologically active endogenously-secreted plasma GLP-1. In humans, sitagliptin, both after a single dose and after once-daily dose for 10 days, resulted in about 2-fold increase in aGLP-1 post-meal (67, 106). Furthermore, sitagliptin decreased total GLP-1 (tGLP-1) in the presence of increased aGLP-1 (107). However, whether the 2-fold increase in aGLP-1 is sufficient to explain the glucose-lowering effect with reduction of HbA<sub>1c</sub> in patients on chronic sitagliptin therapy is controversial.

If DPP 4 inhibitors did lower blood glucose as a direct consequence of increased aGLP-1 levels, plasma insulin levels would be expected to increase as well. However, fasting and postprandial plasma insulin and C-peptide levels were not different before and after 10 days of DPP 4

inhibition in both healthy and T2DM subjects (106, 108, 109). Indeed, infusions of GLP-1 that result in comparable plasma aGLP-1 levels attained by DPP 4 inhibition do not induce insulin secretion in T2DM (10). Some reviewers noted that with DPP 4 inhibitors, the same amount of insulin is secreted at lower glucose level, or insulinogenic index is improved (110). However, any treatment that lowers plasma glucose without increasing insulin secretion, such as weight loss, metformin or  $\alpha$ -glucosidase inhibitors, also improves insulinogenic indices (111, 112).

Another surprising finding is that DPP4 inhibition does not slow gastric emptying (108) when slowed gastric emptying is a consistent finding with exogenous GLP-1 and exenatide treatments (13, 113). An explanation offered in some reviews is that the degree of elevation of aGLP-1 is not of sufficient magnitude to inhibit gastric emptying (110, 114). But by the same rationale, one can extrapolate that the elevation in aGLP-1 from DPP 4 inhibition is also not sufficient to bring about an increase in insulin secretion (108).

***3. How might DPP 4 inhibition lead to a decline in plasma glucose levels without an increase in insulin secretion?***

DPP 4 inhibition results in lower postprandial plasma glucagon levels (108, 109, 115). However, the reduced glucagon secretion is not evident in the fasting state when it would be most beneficial to decrease nocturnal hepatic glucose output. The post-prandial glucagon suppressive effects of DPP 4 inhibitors, while significantly different from placebo, are small and short-lived and the levels are much higher than in non-diabetic subjects, hence unlikely to account for the full antihyperglycemic effect.

The following is speculation by the authors. Many endogenous compounds are subject to DPP 4 modification, resulting in their activation or inactivation, and any of these unknown qualities might have effects on glucose homeostasis (116, 117). If indeed the glucose-lowering effects of DPP 4 inhibition are mediated by GLP-1, one would expect to see maximum clinical effects of one dose of DPP 4 inhibitor on PPG and insulin levels immediately after a meal when GLP-1 secretion is at its maximum. However, this is not the case as *no* clinical effects on glucose, insulin, glucagon, or C-peptide levels over a 2-hour post-meal period were observed after one dose of sitagliptin (67). However, after 4 weeks of sitagliptin, PPG levels were significantly reduced over a 24-hour period in the treatment group, but insulin and C-peptide levels were comparable between treatment and placebo group (118). This phenomenon may signify accumulation, over time, of one or more DPP 4 products that have effects on glucose uptake.

GLP-1 is known to have effects on the gut-hepatoportals-brain neural axis. Sitagliptin should directly inhibit DPP 4 activity at the level of the vascular endothelium in the gut, resulting in greater activation by GLP-1 of sensory neurons originating in the nodose ganglion, where GLP-1R gene expression has been shown to occur (119, 120). It should also cause higher aGLP-1 levels to enter the portal system after eating with subsequent activation of the vagal hepatic nerves (121). GLP-1R mRNA is present on nerve terminals of the portal vein in rodents (120), and there are GLP-1-modifiable glucose sensors in the hepato-portal bed (122). Dog studies had shown that direct infusion of GLP-1 into the portal vein results in increased glucose uptake (123, 124). However, against gut-neuronal pathways being the likely cause of the improved glucose homeostasis with DPP 4 inhibition is this – gastric emptying is not altered. GLP-1 is thought to influence gastric emptying through interacting with afferent sensory neurons. Therefore, if DPP

4 inhibition were of such magnitude as to influence neuronal pathways through greater GLP-1R activation, one would also expect to see effects on gastric emptying, which is not the case.

***4. Was development of DPP 4 inhibitors, which are not specific for GLP-1 and actually resulted in decreased tGLP-1 secretion, really needed to increase plasma aGLP-1 levels?***

There are other hypoglycemic agents that cause minor increase in plasma GLP-1 levels but was thought to not contribute to their antihyperglycemic effect. Three-day treatment with phenformin resulted in elevated levels of gut-derived glucagon-like immunoreactivity (GLI – measured before a radioimmunoassay specific for GLP-1 was available) both during fasting and in response to intraduodenal glucose infusions in T2DM (125). One-week metformin treatment in healthy subjects resulted in dramatic increases in postprandial GLI levels when compared to baseline (126). Furthermore, a 2-week course of metformin in obese non-diabetic volunteers resulted in statistically significant increased in aGLP-1 levels during an OGTT performed under euglycemic-hyperinsulinemic clamp when compared to baseline (127). aGLP-1 levels during both fasting and post-OGTT did not change after a single 850 mg dose of metformin but were significantly increased after 4 weeks of metformin in obese patients with and without T2DM (128). Subsequently, metformin was found to inhibit DPP 4 activity in patients with T2DM (129). Similarly, metformin was found to decrease DPP 4 activity, increase aGLP-1 levels and improved insulin secretory capability to exogenous GLP-1 administration in diabetic mice (130). But on a molar basis, specific DPP 4 inhibitors are 15-20 times more effective at reducing DPP 4 activity than metformin (130). A recent study of healthy subjects showed that both postprandial tGLP-1 and aGLP-1 levels were increased 2-fold with metformin; aGLP-1 levels were

increased 2-fold but tGLP-1 levels were diminished by a third with sitagliptin; and aGLP-1 levels were increased 4-fold and tGLP-1 increased by 1.6-fold with metformin/sitagliptin (107).

These data suggest that metformin and sitagliptin increase aGLP-1 levels through different mechanisms. Most likely metformin increases GLP-1 levels through both inhibition of DPP 4 and secretion from L cells. The mechanism by which metformin might increase GLP-1 secretion is speculative. Biguanides have been shown to inhibit glucose absorption (131, 132). We hypothesize that this decrease in glucose absorption would prolong exposure of the sweet taste receptors on intestinal L-cells (recently found to be the modulators of GLP-1 secretion from L-cells) to glucose, resulting in the prolonged activation of the sweet taste receptors and secretion of GLP-1 (Figure 2) (62).

Even though metformin increases GLP-1 secretion, it is still unclear whether this increase has any glucose-lowering effect. It is well accepted that metformin lowers glucose levels by suppressing hepatic glucose output, mediated through kinase LKB1 in the liver (133, 134). Therefore, it is also reasonable to ask whether sitagliptin, which increases aGLP-1 by the same amount as metformin, is actually lowering glucose through aGLP-1. However, given the synergistic effect of metformin and sitagliptin, both in terms of increase in aGLP-1 levels and lowering of HbA<sub>1c</sub> (0.8% with sitagliptin alone, 1.3% with metformin alone, and 1.8% with metformin/sitagliptin), combination therapy might actually have a meaningful impact in glucose-lowering through the GLP-1 mechanism (73, 78, 107).

## SUMMARY

Exenatide, as adjuvant therapy in T2DM, lead to sustained HbA<sub>1c</sub> reduction of 1.0%, improved  $\beta$  cell function, and weight loss. It is inconvenient to use, but long-acting forms with once-weekly injection, such as exenatide LAR, are under development (135). Liraglutide lowered HbA<sub>1c</sub> by 1.5% in a 14-week study, but phase 3 studies are not yet available in peer-reviewed journals.

The advantage of DPP 4 inhibitors is their availability in oral form. Sitagliptin monotherapy led to HbA<sub>1c</sub> reduction of 0.6-0.7% after 54 weeks. Vildagliptin monotherapy lowered HbA<sub>1c</sub> by 0.9-1.4% after 24 weeks. However, patients with mild T2DM on low dose vildagliptin showed a return of HbA<sub>1c</sub> to pre-treatment levels after 108 weeks. Similar trend was seen in sitagliptin. Long-term data on sitagliptin and vildagliptin are needed to evaluate whether their glucose-lowering effects are sustained. Both DPP 4 inhibitors are weight neutral, and their effects on other DPP 4 substrates needs further research.

A better understanding of the effects of GLP-1 and GLP-1 mimetics on  $\beta$  cell mass in humans and the mechanism of action by which they lower glucagon secretion from  $\alpha$  cells are needed. Finally, more work is needed to elucidate how DPP 4 inhibitors improve insulin sensitivity in humans.

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Prior glycemic treatment	Length	Trial design	Intervention	# subjects randomized	# subjects completed	Baseline HbA <sub>1c</sub> (%)	Baseline FPG (mg/dL)	Δ HbA <sub>1c</sub> (% baseline)	% achieved HbA <sub>1c</sub> ≤ 7%	Δ FPG (mg/dL) baseline	Δ weight (lbs) baseline
<b>EXENATIDE</b>											
Sulfonylurea (34) (Trial A)	30-wk	Randomized, triple-blind, placebo-controlled	Placebo + sulfonylurea	123	74	8.7(1.2)	194(58)	+0.1±0.1	9	+7.2±5.4	-0.6±0.3
			Exenatide 5μg bid + sulfonylurea	125	95	8.5(1.1)	180(45)	-0.5±0.1	33	-5.4±3.6	-0.9±0.3
			Exenatide 10 μg bid + sulfonylurea	129	91	8.6(1.2)	178(50)	-0.9±0.1	41	-10.8±5.4	-1.6±0.3
Metformin (33) (Trial B)	30-wk	Randomized, triple-blind, placebo-controlled	placebo + metformin	113	89	8.2(1.0)	170(40)	+0.1±0.1	13	+14.4±4.2	-0.3±0.3
			Exenatide 5μg bid + metformin	110	90	8.3(1.1)	176(43)	-0.4±0.1	32	-7.2±4.6	-1.6±0.4
			Exenatide 10 μg bid + metformin	113	93	8.2(1.0)	168(46)	-0.8±0.1	46	-10.1±4.4	-2.8±0.5
Sulfonylurea/ metformin (35) (Trial C)	30-wk	Randomized, double-blind, placebo-controlled	placebo + metformin/ sulfonylurea	247	188	8.5(1.0)	180(49)	+0.2±0.1	9	+14.4±3.6	-0.9±0.2
			Exenatide 5μg bid + metformin/ sulfonylurea	245	206	8.5(1.0)	182(52)	-0.6±0.1	27	-9.0±3.6	-1.6±0.2
			Exenatide 10 μg bid + metformin/ sulfonylurea	241	199	8.5(1.1)	178(43)	-0.8±0.1	34	-10.8±3.6	-1.6±0.2
TZD with/without metformin (36)	16-wk	Randomized, double-blind, placebo-controlled	Placebo + TZD with/without metformin	112	96	7.9(0.8)	159(34)	+0.1±0.1	16	+1.8±3.8	-0.2±0.3
			Exenatide 10 μg bid + TZD with/without metformin	121	86	7.9(0.9)	164 (47)	-0.9±0.1	62	-28.6±4.0	-1.8±0.3
Sulfonylurea/ Metformin (37)	26-wk	Randomized, open-label, controlled	Exenatide 10 μg bid + metformin/ sulfonylurea	282	228	8.2(1.0)	182(47)	-1.1	46	-25.7	-2.3
			Glargine ~ 25U/day + metformin/ sulfonylurea	267	242	8.3 (1.0)	187(52)	-1.1	48	-51.5	+1.8
Sulfonylurea/ metformin (38)	52-wk	Randomized, open-label, non-inferiority	Exenatide 10 μg bid + metformin/sulfonylurea	253	199	8.6(1.0)	198(49)	-1.0±0.1	32	-32.4±3.6	-2.5±0.2
			Biphasic aspart (30% insulin aspart) + metformin/sulfonylurea	248	223	8.6(1.1)	203(50)	-0.9±0.1	24	-30.6±3.6	+2.9±0.2

Metformin and/or sulfonylurea (39)	≥ 3 yrs	Trials A, B and C (above) and their open-label extensions were folded into one open-ended, open-label trial		Exenatide 10 µg bid + metformin and/or sulfonylurea	527	217	8.2(1.0)	172(45)	-1.0±0.1	46	-23.5±3.8	-5.3±0.4
<b>LIRAGLUTIDE</b>												
Two or less oral hypoglycemic agents (except TZD) (44)	5-wk	Randomized, double-blind (liraglutide titration 0.5 to 2.0mg in 0.5mg increment weekly) + 2-wk run-in with metformin	Liraglutide + metformin 1,000 mg bid	36	34	9.5(1.0)	238(45)	-0.8 <sup>a</sup>	--	-70.2 <sup>a</sup>	-2.2	
			Liraglutide + placebo	36	30	9.4(0.8)	239(45)	-0.2 <sup>a</sup>	--	-25.2 <sup>a</sup>	-2.1	
			Metformin 1,000 mg bid + placebo	36	25	9.4(0.8)	243(52)	--	--	--	-1.7	
		Randomized, open label	Metformin 1,000 mg bid + Glimepiride 4 mg qd	36	36	9.4(1.2)	234(47)	-0.3 <sup>b</sup>	--	-21.6 <sup>b</sup>	+0.8	
One oral hypoglycemic agent (45)	14-wk	Randomized, double-blind, placebo-controlled (previous hypoglycemic agent discontinued)	Placebo	40	29	8.2(0.7)	203(40)	+0.3	5	--	--	
			Liraglutide 0.65 mg qd	40	35	8.1(0.6)	203(49)	-1.0	38	-48.6 <sup>c</sup>	--	
			Liraglutide 1.25 mg qd	42	39	8.3(0.8)	214(43)	-1.4	48	-61.2 <sup>c</sup>	--	
			Liraglutide 1.90 mg qd	41	37	8.5(0.9)	221(56)	-1.5	46	-61.2 <sup>c</sup>	-3.0	
<b>SITAGLIPTIN</b>												
Diet or one oral hypoglycemic agent (72, 77)	24-wk	Randomized, double-blind, placebo-controlled (washout period)	Placebo	253	216	8.0(0.8)	176.4(41.4)	+0.2	17	+5.4	-1.1±0.2	
			Sitagliptin 100 mg qd	238	209	8.0(0.9)	171.0(43.2)	-0.6	41	-12.6	-0.2±0.2	
			Sitagliptin 200 mg qd	250	214	8.1(0.9)	174.6(45.0)	-0.8	45	-16.2	-0.1±0.2	
	30-wk extension	randomized	Sitagliptin 100 mg qd	188	--	7.9	--	-0.6	41	--	--	
			Sitagliptin 200 mg qd	194	--	8.0	--	-0.6	46	--	--	

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Diet and exercise (73, 78)	24-wk	Randomized, double-blind, placebo-controlled, parallel-group	Placebo	176	127	8.7(1.0)	196.3(47.4)	+0.2	9	+5.8	-0.9
			Sitagliptin 100 mg qd	179	142	8.9(1.0)	201.4(49.4)	-0.7	20	-17.5	0.0
			Metformin 500 mg bid	182	153	8.9(1.0)	205.2(50.6)	-0.8	23	-27.3	
			Metformin 1,000 mg bid	182	156	8.7(0.9)	197.0(46.8)	-1.1	38	-29.3	-0.6 to -1.3
			Sitagliptin 50mg bid + metformin 500 mg bid	190	164	8.8(1.0)	203.9(51.7)	-1.4	43	-47.1	
			Sitagliptin 50 mg bid + metformin 1,000 mg bid	182	164	8.8(1.0)	196.7(48.2)	-1.9	66	-63.9	
	30-wk Extension	Double-blind, active- controlled phase	Sitagliptin 100 mg qd	100	--		--	-0.8	23	--	--
			Metformin 500 mg bid	122	--		--	-1.0	25	--	--
			Metformin 1,000 mg bid	137	--	Mean HbA <sub>1c</sub> 8.7%	--	-1.3	44	--	--
			Sitagliptin 50mg bid + metformin 500 mg bid	148	--		--	-1.4	48	--	--
Sitagliptin 50 mg bid + metformin 1,000 mg bid			157	--		--	-1.8	67	--	--	
Pioglitazone (74)	24-wk	Randomized, double-blind, placebo-controlled, parallel-group	Placebo + pioglitazone 30-45 mg qd	178	158	8.0(0.8)	165.6(39.9)	-0.2	23	+1.0	+1.5
			Sitagliptin 100 mg qd + pioglitazone 30-45 mg qd	175	149	8.1(0.8)	168.3(39.5)	-0.9	45	-16.7	+1.8
Metformin (75)	24-wk	Randomized, double-blind, placebo-controlled, parallel-group	Placebo + metformin ≥ 1,500 mg/day	237	192	8.0(0.8)	172.8(41.4)	0.0	18	+9.0	--
			Sitagliptin 100 mg qd + metformin ≥ 1,500mg/day	464	416	8.0(0.8)	169.2(41.4)	-0.7	47	-16.2	--
	30-wk Extension	Double-blind, active- controlled (placebo switched to glipizide)	Glipizide 5-15 mg/day + metformin ≥ 1,500mg/day	157	--	7.9	--	-0.9	61	--	+1.5
			Sitagliptin 100 mg qd + metformin ≥ 1,500mg/day	387	--	7.9	--	-0.7	51	--	-0.9

Glimepiride or glimepiride/metformin(76)	24-wk	Randomized, double-blind, placebo-controlled, parallel-group	Placebo + glimepiride ≥ 4mg/day	106	87	8.4(0.8)	184.9(42.3)	+0.3	9	+18.4	0.0
			Placebo+ Glimepiride ≥ 4mg/day + metformin ≥ 1,500mg/day	113	92	8.3(0.7)	178.4(42.6)	+0.3	1	+12.9	-0.7
			Sitagliptin 100 mg qd + glimepiride ≥ 4mg/day	106	83	8.4(0.8)	182.6(33.1)	-0.3	11	-0.88	+1.1
			Sitagliptin 100 mg qd + glimepiride ≥ 4mg/day + metformin ≥ 1,500mg/day	116	102	8.3(0.7)	179.4(41.6)	-0.6	23	-7.8	+0.4
metformin(80)	52-wk	Randomized, double-blind, active-controlled, parallel-group, non-inferiority trial	Sitagliptin 100 mg qd + metformin ≥ 1,500mg/day	588	386	7.5(0.8)	157.7(33.7)	-0.7	63	-10.1	-1.5
			Glipizide 5-20 mg/day + metformin ≥ 1,500mg/day	584	412	7.5(0.9)	159.1(38.5)	-0.7	59	-7.6	+1.1
<b>VILDAGLIPTIN</b>											
Drug-naïve (91, 92)	52-wk	randomized, double-blind, placebo-controlled, parallel-group	Placebo	150	131	6.8(0.4)	129.6 (21.6)	+0.1±0.1	--	+9.0 ±1.8	-0.2±0.3
			Vildagliptin 50 mg qd	156	133	6.7(0.4)	127.8 (21.6)	-0.2±0.1	--	+3.6±1.8	-0.5±0.3
	4-wk washout, 52-wk ext		Placebo	63	50	6.7 (0.4)	126.0(18.0)	+0.5±0.1	--	+21.6±5.4	-0.3±0.4
			Vildagliptin 50 mg qd	68	58	6.6 (0.4)	122.4(18.0)	+0.1±0.1	--	+10.8±5.4	-1.1±0.5
Drug-naïve (93)	24-wk	randomized, double-blind, placebo-controlled, parallel-group	placebo	160	119	8.4(0.8)	178.2(45.0)	-0.3±0.1	--	-1.8	-1.4±0.4
			vildagliptin 50 mg qd	163	130	8.2(0.8)	176.4(43.2)	-0.8±0.1	--	-18.0	-1.8±0.4
			vildagliptin 50 mg bid	152	128	8.6(0.8)	181.8(39.6)	-0.8±0.1	--	-14.4	-0.3±0.4
			vildagliptin 100 mg qd	157	134	8.4(0.8)	178.2(41.4)	-0.9±0.1	--	-14.4	-0.8±0.4
Drug naïve (94)	52-wk	randomized, double-blind, active-controlled, parallel-group	vildagliptin 50 mg bid	526	378	8.7(1.1)	189.0(52.2)	-1.0±0.1	--	-16.2±1.8	+0.3±0.2
			metformin 1000 mg bid	254	191	8.7(1.1)	189.0(52.2)	-1.4±0.1	--	-34.2±3.6	-1.9±0.3

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Drug naïve (95)	24-wk	randomized, double-blind, active-controlled, parallel-group	vildagliptin 50 mg bid	519	446	8.7(1.1)	185.4(48.6)	-1.1±0.1	--	-23.4±1.8	-0.3±0.2									
			rosiglitazone 8 mg qd	267	232	8.7(1.1)	185.4(52.2)	-1.3±0.1	--	-41.4±3.6	+1.6±0.3									
Drug naïve (96)	24-wk	randomized, double-blind, active-controlled, parallel-group	pioglitazone 30 mg qd	161	133	8.7(1.0)	189.0(55.8)	-1.4±0.1	43	-34.2±3.6	+1.5±0.3									
			vildagliptin 50 mg qd + pioglitazone 15 mg qd	144	115	8.8(0.9)	192.6(48.6)	-1.7±0.1	54	-43.2±3.6	+1.4±0.3									
			vildagliptin 100 mg qd + pioglitazone 30 mg qd	148	129	8.8(1.1)	196.2(48.6)	-1.9±0.1	65	-50.4±3.6	+2.1±0.3									
			vildagliptin 100 mg qd	154	136	8.6(1.0)	190.8(48.6)	-1.1±0.1	43	-23.4±3.6	+0.2±0.3									
Drug naïve (97)	24-wk	randomized, double-blind, active-controlled, parallel-group	vildagliptin 50 mg bid	441	399	8.6 (0.9)	180.0(43.2)	-1.4±0.1	46	-21.6±1.8	-0.4±0.1									
			acarbose up to 100 mg tid	220	192	8.6 (1.0)	183.6(45.0)	-1.3±0.1	47	-27.0±3.6	-1.7±0.2									
sulfonylurea(98)	24-wk	randomized, double-blind, placebo-controlled	placebo + glimepiride 4mg qd	176	108	8.5(1.0)	185.4(52.2)	+0.1±0.1	12	+3.6±3.6	-0.4±0.3									
			vildagliptin 50 mg qd + glimepiride 4mg qd	170	113	8.5(0.9)	189.0(54.0)	-0.6±0.1	21	-5.4±3.6	-0.1±0.3									
			vildagliptin 50 mg bid + glimepiride 4mg qd	169	111	8.6(1.0)	189.0(48.6)	-0.6±0.1	25	-7.2±3.6	+1.3±0.3									
metformin(99)	24-wk	randomized, double-blind, placebo-controlled, parallel-group	placebo + metformin ≥ 1,500 mg/day	182	152	8.3(0.9)	181.8(43.2)	+0.2±0.1	<table border="1"> <thead> <tr> <th colspan="2">baseline HbA<sub>1c</sub></th> </tr> </thead> <tbody> <tr> <td>≤7.9</td> <td>14</td> </tr> <tr> <td>7.9-8.5</td> <td>13</td> </tr> <tr> <td>&gt;8.5</td> <td>2</td> </tr> </tbody> </table>		baseline HbA <sub>1c</sub>		≤7.9	14	7.9-8.5	13	>8.5	2	--	--
			baseline HbA <sub>1c</sub>																	
			≤7.9	14																
			7.9-8.5	13																
			>8.5	2																
			vildagliptin 50 mg qd + metformin ≥1,500 mg/day	177	153	8.4(0.9)	174.6(39.6)	-0.5±0.1	<table border="1"> <thead> <tr> <th colspan="2">baseline HbA<sub>1c</sub></th> </tr> </thead> <tbody> <tr> <td>≤7.9</td> <td>50</td> </tr> <tr> <td>7.9-8.5</td> <td>22</td> </tr> <tr> <td>&gt;8.5</td> <td>8</td> </tr> </tbody> </table>		baseline HbA <sub>1c</sub>		≤7.9	50	7.9-8.5	22	>8.5	8	--	--
baseline HbA <sub>1c</sub>																				
≤7.9	50																			
7.9-8.5	22																			
>8.5	8																			
vildagliptin 50 mg bid + metformin ≥1,500 mg/day	185	157	8.4(1.0)	178.2(46.8)	-0.9±0.1	<table border="1"> <thead> <tr> <th colspan="2">baseline HbA<sub>1c</sub></th> </tr> </thead> <tbody> <tr> <td>≤7.9</td> <td>54</td> </tr> <tr> <td>7.9-8.5</td> <td>31</td> </tr> <tr> <td>&gt;8.5</td> <td>16</td> </tr> </tbody> </table>		baseline HbA <sub>1c</sub>		≤7.9	54	7.9-8.5	31	>8.5	16	-	--			
baseline HbA <sub>1c</sub>																				
≤7.9	54																			
7.9-8.5	31																			
>8.5	16																			

TZD(100)	24-wk	randomized, double-blind, placebo-controlled, parallel-group	placebo + pioglitazone 45 mg qd	158	128	8.7(1.2)	181.8(54.0)	-0.3±0.1	15	-9.0±3.6	--
			vildagliptin 50 mg qd + pioglitazone 45 mg qd	147	124	8.6(1.0)	185.4(52.2)	-0.8±0.1	29	-14.4±3.6	--
			vildagliptin 50 mg bid + pioglitazone 45 mg qd	158	124	8.7(1.2)	180.0(59.4)	-1.0±0.1	36	-19.8±3.6	--
insulin(101)	24-wk	randomized, double-blind, placebo-controlled, parallel-group	placebo + insulin	152	124	8.4(1.1)	156.6(55.8)	-0.2±0.1	--	-3.6±-7.2	0.6±0.3
			vildagliptin 50 mg bid + insulin	144	114	8.4(1.0)	167.4(55.8)	-0.5±0.1	--	-14.4±5.4	1.3±0.3
metformin(102)	24-wk	randomized, double-blind, active-controlled	vildagliptin 50 mg bid + metformin ≥1,500 mg/day	295	262	8.4(1.0)	196.2(46.8)	-0.9±0.1	27%	-25.2±1.8	+0.3±0.2
			pioglitazone 30 mg qd + metformin ≥1,500 mg/day	281	244	8.4(0.9)	198.0(48.6)	-1.0±0.1	36%	-37.8±1.8	+1.9±0.2

Data presented as mean (SD), or mean ± SE

TZD = thiazolidinedione

<sup>a</sup> change relative to metformin therapy

<sup>b</sup> change relative to liraglutide and metformin combination therapy

<sup>c</sup> change relative to placebo

**Table 1: Summaries of selected clinical trials on exenatide, liraglutide, sitagliptin, and vildagliptin.**

**Fig.1 Structure of native GLP-1, exenatide, liraglutide, sitagliptin, and vildagliptin.** The N-terminal dipeptide "HA" of GLP-1 is cleaved by dipeptidyl peptidase 4 (DPP 4) and the remaining fragment does not increase insulin secretion. For exenatide, the substitution of glycine for alanine at position 8 prevents the degradation by DPP 4. The free fatty acid derivative that is attached to liraglutide is thought to promote non-covalent binding of liraglutide to albumin.

**Fig. 2 Mechanism of action of sitagliptin and exenatide.** GLP-1 is released from L cells (stained red) of the gut and is subject to DPP 4 (stained green on endothelial cells of blood vessels of the gut) degradation in both gut and blood. Sitagliptin and vildagliptin inhibit DPP 4 action in blood and on endothelial cells. Metformin, orlistat and  $\alpha$ -glucosidase inhibitors increase GLP-1 secretion. Exenatide, a GLP-1 receptor agonist, increases insulin secretion from  $\beta$  cells (stained green) in islets of Langerhans. The  $\alpha$  cells in islets are stained red.

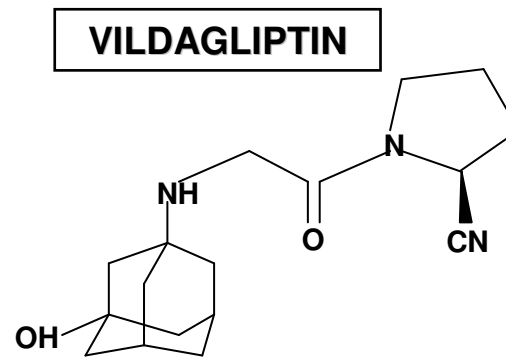
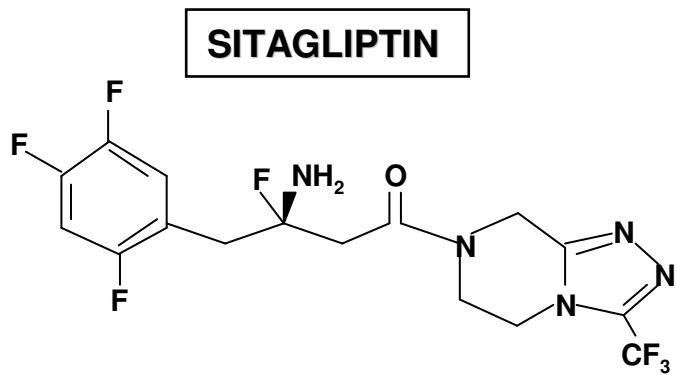
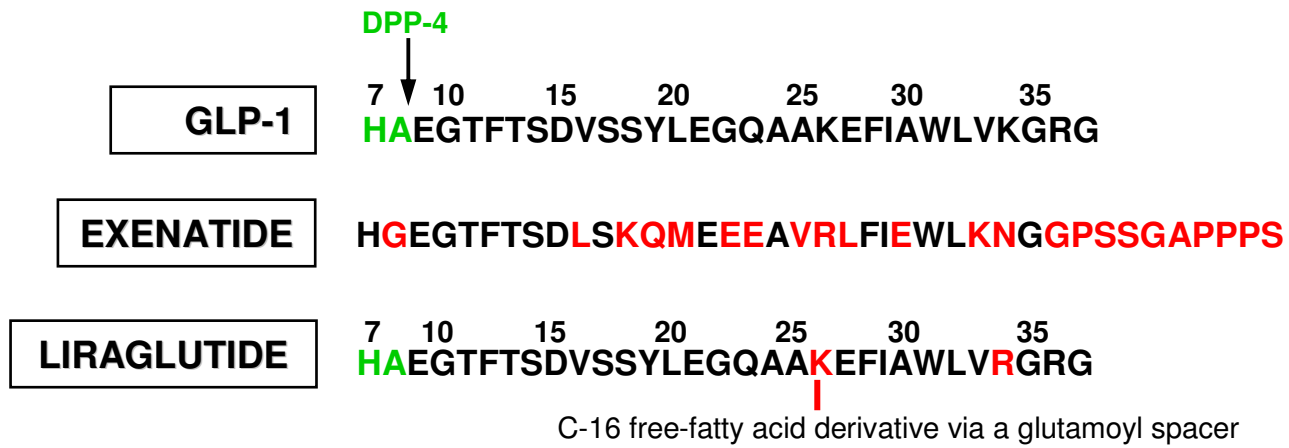


Fig. 1

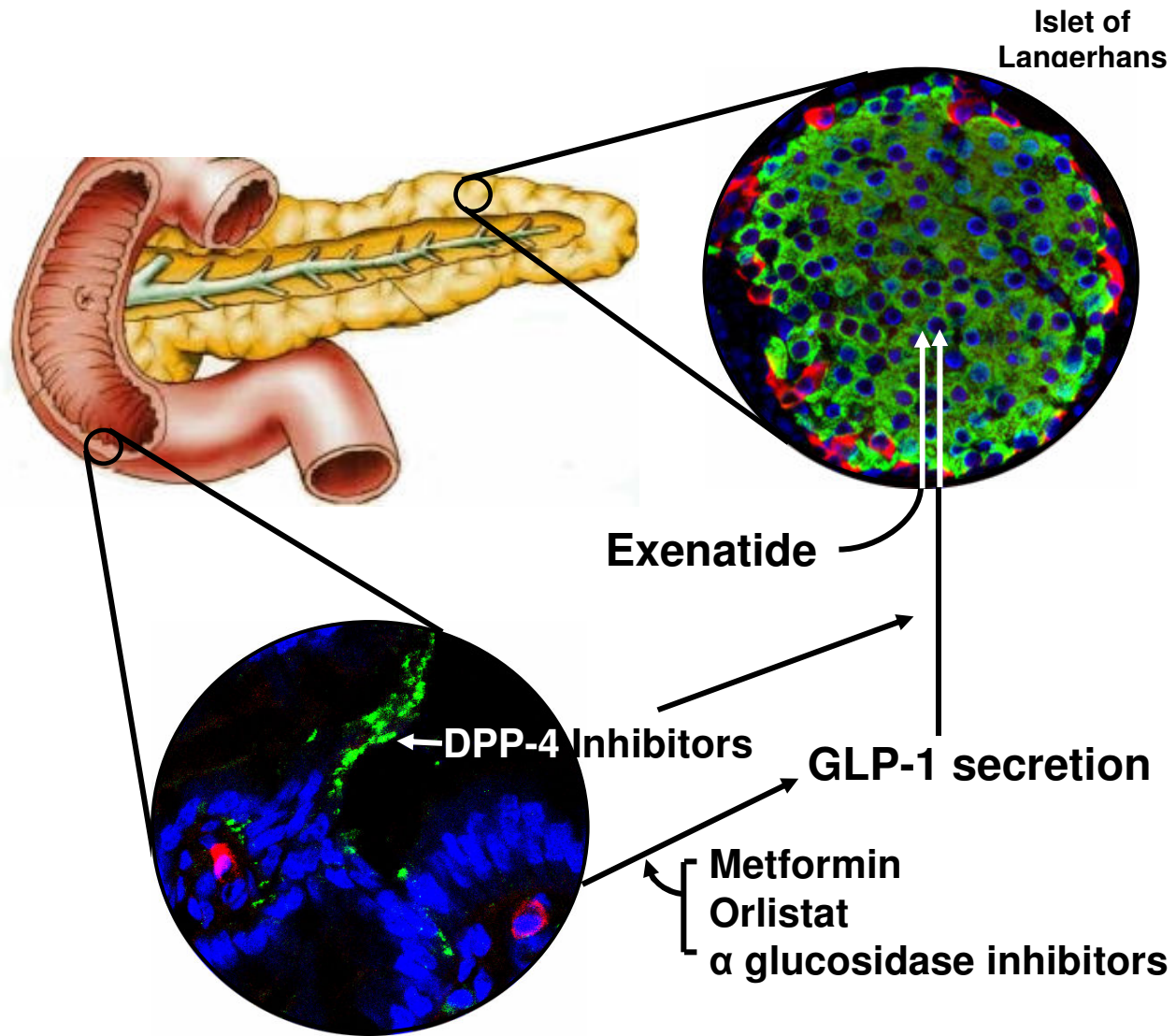


Fig. 2