Comparison of efficacy between different incretin-based therapies; GLP-1 agonists and DPP-4 inhibitors.

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Type 2 diabetes mellitus is widely prevalent and is often co-existent with obesity. Many of the available treatment options have side effects such as weight gain which often affect patients’ willingness to continue the treatment. Incretin-based therapies for type 2 diabetes offer many advantages over conventional therapies. In particular effective weight loss, lack of significant hypoglycaemia, and favourable cardiometabolic profile make them very attractive treatment options for patients with type 2 diabetes mellitus. Incretin-based therapies are available as either incretin mimetics (also called GLP-1 agonists) or incretin enhancers (DPP-4 inhibitors). Although agents in both these classes of incretin-based therapy are effective through a common GLP-1 pathway, there are many differences amongst them including the route of administration, frequency of administration, effects on body weight, and extent of glycaemic improvement. There are several trials evaluating these individual incretin-based agents either as monotherapy or in combination with other anti-diabetic agents, however very few have looked into direct comparison amongst the agents in these two classes. This review is aimed to look at important mechanistic differences between incretin mimetics and enhancers and impact of these differences on glycaemic, weight and other cardiometabolic parameters.

Keywords: GLP-1 analogues, GLP-1 agonists, DPP-4 inhibitors, incretins, head-to-head comparison, patient satisfaction
INTRODUCTION

Prevalence of type-2 diabetes mellitus (T2DM) is rapidly increasing worldwide. The International Diabetes Federation (IDF) estimates the current prevalence of diabetes at around 285 million which is estimated to increase to 439 million cases of diabetes and 472 million cases of impaired glucose tolerance (IGT) by 2030.\(^1\) Similarly there has been an uptrend in adiposity worldwide.\(^2\) The National Obesity Observatory data estimates the prevalence of obesity in the UK at 23%, whilst 61% of adults are overweight.\(^3\) The majority of patients with T2DM are obese\(^4\) and many of the current therapeutic options for management of T2DM can cause further weight gain.\(^5,6\) Concerns about weight gain adversely affect patients’ willingness to begin and continue treatment with glucose-lowering medications such as thiazolidinediones (TZDs), insulin, and sulphonylureas (SU).\(^7\) Often patients’ quality of life can be negatively affected by the underlying disease process and its complications such as polypharmacy, weight gain, hypoglycaemia and micro- and macrovascular complications.\(^8\) Recently introduced incretin-based therapies appears to offer advantages over conventional therapies by either keeping the weight steady or even achieving weight loss, limiting hypoglycaemia, whilst achieving effective glycaemic control. This review is to look at the comparisons between two classes of incretin-based therapies, DPP-4 inhibitors (incretin enhancers) and glucagon-like peptide-1 (GLP-1) agonists (incretin mimetics) focusing on head-to-head comparisons of efficacy, tolerability and safety profile between the agents from these two classes.

PHYSIOLOGY OF INCRETINS

Glucagon-like peptide-1 and glucose-dependent insulinoceptive polypeptide (GIP), two major gut hormones are secreted into the circulation by “L” and “K” cells of small intestine
respectively, in response to oral food ingestion. These hormones are called incretins and account for 50–70% of post-prandial insulin release, thus impacting on post-prandial glucose (PPG) control. Also as insulin release is glucose dependent, this minimises the risk of hypoglycaemia. Apart from insulinotropic effects, GLP-1 also suppresses glucagon release, reduces hepatic gluconeogenesis, delays gastric emptying, and reduces food intake by promoting satiety. These effects are mediated via stimulation of GLP-1 receptors present in various locations in the body including pancreatic alpha, beta cells, GI tract, endothelium, heart, kidneys, lungs and brain. The classic “incretin effect” refers to the observation that oral glucose elicits a higher insulin response compared to the intravenous glucose at the similar plasma glucose concentration. The impaired incretin effect in patients with T2DM is thought to be multifactorial. Reduced post-prandial GLP-1 response, and a reduced insulinotropic response are some of the contributing factors. In a study comparing healthy subjects with patients with T2DM, lack of the incretin effect in spite of comparable GLP-1 as well as GIP secretion was observed. Administration of GLP-1 subcutaneously over 6 weeks in patients with T2DM has been shown to improve glycaemic control, insulin sensitivity, and beta cell function along with reduced gastric emptying and reduction in bodyweight.

**INCRETIN-BASED THERAPIES**

Due to various favourable cardiometabolic and insulinotropic effects, GLP-1 is a very attractive candidate as a therapeutic intervention in management of T2DM. GLP-1 however has a very short half-life and as such is unsuitable for routine clinical use as it need to be administered via continuous subcutaneous infusion. GLP-1 has a half-life of a few minutes as it is broken down by endopeptidases enzymes such as dipeptidyl peptidase-4 (DPP-4) which has ubiquitous presence in the human body. As the native GLP-1 molecule is
unsuitable for routine clinical use, stimulation of GLP-1 receptors either by administration of engineered GLP-1 agonists or restoring endogenous GLP-1 pool by inhibiting its DPP-4 mediated breakdown are the two approaches to obtain or maintain high levels of GLP-1. (9)

INCRETIN MIMETICS

GLP-1 agonists mimicking endogenous GLP-1 in their pharmacokinetic and pharmacological properties are termed incretin mimetics. These are modified GLP-1 molecules and are resistant to DPP-4 induced degradation. These stimulate GLP-1 receptors at pharmacological levels resulting in GLP-1 activity much higher than expected from normal physiological stimulation. Exenatide administered twice daily was the first GLP-1 agonist to become available for clinical use and was approved by US Food and Drug Administration (FDA) in April 2005 and by the European Medicine Agency (EMA) in November 2006. (21) It was first isolated from the saliva of Heloderma suspectum lizard (Exendin-4). (22) Exendin-4 bears 53% sequence homology to the human GLP-1 yet it is resistant to degradation by mammalian DPP-4 and has a plasma half-life of 2.4 h. It is available in 5 and 10 mcg formulations for twice-daily subcutaneous administration timed around meals. Liraglutide; the first human GLP-1 analogue has 97% amino acids sequence homology with native GLP-1 and fatty chain addition to its molecule prolongs its half-life to 13 hrs (23). Recently a long-acting, once-weekly preparation of exenatide (Bydureon) at dose of 2 mg has been approved for clinical use by the EMA in Europe. Encapsulating the injectable microspheres allows a controlled release of the exenatide. A steady state of exenatide is generally achieved by 6–10 weeks of therapy. (24)
INCRETIN ENHANCERS

DPP-4 inhibitors prolong the half-life and availability of endogenous GLP-1 by inhibiting the DPP 4 and therefore termed as incretin enhancers. Sitagliptin was the first DPP-4 inhibitor approved for clinical use in October 2006 and is available in 100 mg tablet for once-daily use. It selectively and reversibly binds to active site of DPP-4 rendering it unavailable for removal of the N-terminal of GLP-1. Saxagliptin is the second DPP-4 inhibitor approved for the clinical use for both the US and the European markets. It is available as a once-daily tablet of 2.5 and 5 mg which can be taken irrespective of meal times. Saxagliptin is approved for use in varying degrees or renal impairment. Three other DPP-4 inhibitors have been approved for clinical use in specific geographical markets. Vildagliptin has market approval in Europe; alogliptin has market approval in Japan, whilst linagliptin has recently gained approval for clinical use in the US as well as in Europe. All the DPP-4 inhibitors presently available are administered orally. Currently other GLP-1 agonists (e.g., lixisenatide and albiglutide and DPP-4 inhibitors are at various stages of development and in clinical trials programme. Taspoglutide was another once-a-week human GLP-1 analogue in development but further trials have been suspended in the late stages due to agent specific hypersensitivity reactions.

COMPARISONS BETWEEN INCRETIN MIMETICS (GLP-1 AGONISTS) AND INCRETIN ENHANCERS (DPP-4 INHIBITORS)

Agents in both these classes have been studied as monotherapy or in combination with other anti-diabetic medications. DPP-4 inhibitors are administered orally, once-a-day as compared to GLP-1 agonists which are administered subcutaneously, once- or twice-a-day or more recently once-a-week. GLP-1 agonists slow gastric emptying in addition to a reduction in
appetite however DPP-4 inhibitors do not seem to have these effects.\textsuperscript{(27)} In general the observation is that GLP-1 agonists have been found to be more effective in glycaemic management and weight reduction as compared to DPP-4 inhibitors. However there are a limited number of head-to-head studies directly comparing the effects of DPP-4 inhibitors and GLP-1 agonists. The first data suggesting key differences between DPP-4 inhibitors and GLP-1 agonists comes from an initial short-term proof of concept study suggesting important mechanistic differences between exenatide BID and sitagliptin. Since then the longer term randomised control trials (RCTs) have compared these two classes of therapeutic agents as summarised in Table 1.

THE “PROOF OF CONCEPT” STUDY

In a short double-blind, double-dummy, cross-over study involving 61 patients with metformin-treated T2DM, a two-week therapy with exenatide (5 mcg twice daily for the first week increasing to 10 mcg twice daily for second week) was associated with greater improvement in 2 hours PPG as compared to that obtained with a two-week therapy with sitagliptin at 100 mg once daily.\textsuperscript{(28)} More importantly, sitagliptin-treated patients noticed further improvement in PPG levels after changing over to exenatide suggesting superiority of exenatide to improve post-prandial hyperglycaemia, an effect of increased post-prandial insulin release associated with GLP-1 receptor agonists. There was no statistically significant difference in the improvement achieved by both agents in fasting-plasma glucose (FPG). The differential mechanistic effects are summarised in Table 2.

Patients’ gastric emptying rates were also assessed using 1000 mg of an oral liquid acetaminophen preparation. Exenatide significantly slowed gastric emptying compared to sitagliptin ($p < .0001$). Exenatide-treated patients were also found to exhibit a reduction in the
calorie intake as assessed by ad libitum meal. There was reduced calorie intake of averaging 134 kcal less in the exenatide treated group as compared to the sitagliptin treated group. Due to variability of the calorie intake, median caloric intake was assessed which showed a similar trend (exenatide: –138 kcal vs. sitagliptin: +63 kcal).

During this two-week trial the mean postprandial glucagon concentration relative to baseline was reduced in both treatment groups, the reduction in post-prandial glucagon following exenatide was significantly greater compared to sitagliptin (\( p = .0011 \)). There was an increase in insulinogenic index of insulin secretion with exenatide compared to sitagliptin (ratio exenatide to sitagliptin: 1.50 ± .26, \( p = .0239 \)). Nausea was the predominant side effect and experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin.\(^{(28)}\)

A more recent study comparing both of the above therapies given for 8 weeks in patients with T2DM (HbA1c of 8.3± 1.0% and body mass index of 35 ± 5 kg/m\(^2\)) revealed a reduction in postprandial glucagon secretion and improvement in homeostasis model assessment of beta-cell function (HOMA-B) with exenatide 10 mcg twice daily as well as sitagliptin 100 mg daily, however the improvement was significantly more in exenatide treated patients in comparison to the sitagliptin treated group.\(^{(29)}\) Both exenatide and sitagliptin therapies resulted in an improvement in 2h-PPG, average 24-h glucose and the time spent with glucose between 3.9 and 7.8 mmol/L over a 24-hour period. However exenatide therapy was associated with significantly lower 2hr-PPG, average 24-hour glucose and more time spent with glucose between 3.9-7.8 mmol/l (\( p \leq .05 \)). As recently appreciated in other studies, post prandial intact GLP-1 levels were reduced with exenatide therapy and
increased with sitagliptin. Post-prandial glucagon levels were reduced significantly more by exenatide therapy than sitagliptin ($p \leq 0.005$). (29)

To summarise, there appears to be important mechanistic differences between exenatide and sitagliptin in these short-term studies. But longer-term, direct head-to-head comparative studies are needed to ascertain durability and effects of these differences on the glycaemic outcomes. Also, it is important to ascertain these differential effects extend to the other agents in the respective incretin-based classes.

**HEAD-TO-HEAD RCTs OF GLP-1 AGONISTS AND DPP-4 INHIBITORS**

The effect of these physiological differences were studied in four further randomised studies; each lasting for 24–26 weeks with one of them having a further extension period of 26 weeks. (Table 1)

The 1860-Lira-DPP-4 study was an open-label parallel group trial comparing liraglutide (1.8 and 1.2 mg) against sitagliptin (100 mg) all in combination with metformin in subjects with T2DM treated patients with type 2 diabetes. (30) Recently the outcomes of an open-label extension for further 26 weeks in patients completing the 1860-Lira-DPP-4 study have been published. (31) Therefore the 1860-Lira-DPP-4 study comparing liraglutide 1.2 and 1.8 mg with sitagliptin 100 mg is the longest head-to-head comparative study between a GLP-1 agonists and DPP-4 inhibitor.

The DURATION 2 (Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly) and DURATION 4 trials involved comparison of a recently approved once weekly preparation of exenatide (Exenatide LAR 2mg) against sitagliptin (100 mg/day). (32, 33) The DURATION-4
was a monotherapy study whilst the DURATION-2 involved combination therapy with metformin and also had a third arm involving Pioglitazone. In a T-emerge 4-trial, taspoglutide, a once-weekly GLP-1 analogue was compared against sitagliptin in a double-dummy 24-week trial. (34) Taspoglutide was suspended in the late stages of development due to concerns regarding hypersensitivity reactions and gastrointestinal side effects. (35)

Changes in HbA1c

In the 1860-Lira-DPP-4 study, mean baseline HbA1c was 8.4%. A greater reduction in HbA1c was seen with liraglutide 1.2 mg (−1.24%; 95% CI, −1.37 to −1.11) and 1.8 mg (−1.5%; 95% CI, −1.63 to −1.37), compared with sitagliptin (−.9%; 95% CI, −1.03 to −.77). Estimated mean treatment differences for liraglutide at 1.2 and 1.8 mg doses compared to 100 mg sitagliptin were −.34% for 1.2 mg (p < .0001) and −.6% for 1.8 mg (p < .0001). The reduction of .9% in HbA1c with sitagliptin in the 1860-Lira-DPP-4 study is one of the better results achieved in a trial with sitagliptin. (30)

During the extension phase of the 1860-Lira-DPP-4 study, mean HbA1c improvement with liraglutide 1.8 mg, 1.2 mg and sitagliptin at 52 weeks from baseline was 1.29%, 1.51% and .88% respectively. Thus liraglutide produced significant and sustained reduction in HbA1c compared to sitagliptin at 52 weeks. The improvement in the glycaemic control with liraglutide was irrespective of baseline HbA1c. (31)

In the DURATION-2 study, the mean baseline HbA1c was 8.6%. Exenatide LAR therapy resulted in a significantly reduction in HbA1c compared with sitagliptin (−1.5% vs. −.9% p < .0001). Significant HbA1c improvement was noted within 4 weeks of exenatide LAR therapy and within 6 weeks of Sitagliptin therapy. In a subgroup of patients with a basal HbA1c less than 9%, exenatide LAR therapy resulted in significant improvements (mean baseline HbA1c 7.8%, change in HbA1c -1.1%) in comparison to sitagliptin (mean
baseline HbA1c 7.7%, change in HbA1c -0.5%). It is well appreciated that the relative contribution of post-prandial glucose in overall diurnal hyperglycaemia is higher in well-controlled subjects with diabetes. Further improvement in HbA1c in a subgroup of well-controlled patients during the DURATION-2 study therefore suggests underlying improvements in PPG, although PPG was not measured in the study.

In T-emeerge 4 Trial, taspoglutide 10 and 20 mg have been shown to improve HbA1c significantly more than that achieved with sitagliptin. (−1.3%, −1.23% and −0.89% improvement from baseline with taspoglutide 20 mg, 10 mg and sitagliptin respectively. p < .001 for both doses of taspoglutide against sitagliptin). The mean baseline HbA1c across the treatment arms ranged from 7.95–8.03% in this study. Complete data from the DURATION-4 trial has not been published. According to the press release from the manufacturer, 26 weeks of monotherapy with exenatide LAR studied in DURATION-4 trial reduced HbA1c by 1.5% from baseline as opposed to 1.2% reduction with sitagliptin. 

**Changes in Glucose Levels**

In the 1860-Lira-DPP-4 study, the mean reduction in FPG was greater with liraglutide compared to sitagliptin. (mean of −2.14 mmol/L with liraglutide 1.8 mg, −1.87 mmol/L with liraglutide 1.2 mg and −0.83 mmol/L with sitagliptin 100 mg). Improvements and differences in FPG were sustained during extension phase of the 1860-Lira-DPP-4 study. At 52 weeks, the mean reduction if FPG was −2.04 mmol/l, −1.71mmol/l and −0.59 mmol/l with liraglutide 1.8 mg, 1.2 mg and sitagliptin 100 mg, respectively. Treatment differences between sitagliptin and liraglutide remained statistically significant for both doses (p < .0001). The improvement in mean FPG was two-fold greater with exenatide LAR treated patients in comparison to sitagliptin treated patients in DURATION-2 trial.
Changes in post-prandial glucose levels were not assessed in these head-to-head trials. In contrast to short-term mechanistic studies, there was a significant difference in FPG in these head-to-head comparative trials conducted over longer period of time. Differences in efficacy and tolerability amongst studied GLP-1 analogue and DPP-4 inhibitor in the 1860-Lira-DPP-4 and DURATION-2 study are summarised in Table 3.

**Changes in Body Weight**

In the 1860-Lira-DPP-4 study group trial, the mean weight loss was significantly greater with liraglutide than sitagliptin. The estimated mean weight differences were −2.4 kg (95% CI −3.14 to −1.70) for 1.8 mg liraglutide versus sitagliptin, and −1.90 kg (−2.61 to −1.18) for 1.2 mg liraglutide versus sitagliptin. Liraglutide at both doses produced a greater reduction in waist circumference but there were no differences in Waist-Hip ratio. During the 1860-Lira DPP4 extension phase, weight loss achieved during the first 26 weeks was sustained at 52 weeks. At the end of study period mean weight loss with liraglutide 1.8 mg, 1.2 mg and sitagliptin was 3.68, 2.78 and 1.16 kg, respectively with mean treatment differences between the agents remaining statistically significant (p < .0001).

In the DURATION-2 trial, the differences in weight loss became apparent by 4 weeks and by week 26, weight loss with exenatide LAR (−2.3 kg, 95% CI −2.9 to −1.7) was significantly greater compared to sitagliptin (−.8 kg, 95% CI −1.4 to −.1). The mean treatment difference was −1.5 kg (95% CI −2.4 to −.7, adjusted p=.0002) for exenatide LAR versus sitagliptin. In terms of absolute numbers, more than 75% (n=123) of patients on once-weekly exenatide lost body weight, compared with 61% (n=101) of those on sitagliptin. Weight loss with taspoglutide 10 mg and 20 mg once-weekly dose was 1.23 and 2.54 kg.
respectively in comparison to a .55-kg weight loss noticed with sitagliptin over a 24-week study period.\textsuperscript{(34)}

The effect of differential calorie intake and the reduced gastric emptying noticed during short term mechanistic studies between agents in GLP-1 analogue and DPP-4 inhibitors group probably explain the differential weight loss in favour of GLP-1 agonists in the subsequent longer term head -to-head comparisons up to a 1-year period.

**Changes in Blood Pressure and Other Metabolic Parameters**

There was no significant difference observed for systolic blood pressure in 1860-Lira-DPP-4 study group trial although both liraglutide and sitagliptin reduced the systolic blood pressure. Sitagliptin reduced diastolic blood pressure significantly compared to 1.8 mg liraglutide but there was no significant difference compared to 1.2 mg liraglutide. The overall effect on the blood pressure with the either drug was small.\textsuperscript{(30)} During the 1860-Lira-DPP-4 study extension there were no significant differences noted with liraglutide or sitagliptin except reduction of systolic blood pressure with 1.8 mg liraglutide. Other large clinical studies with liraglutide have shown consistent reductions in systolic blood-pressure.\textsuperscript{(37–42)} During the DURATION-2 trial the exenatide LAR treated group had significantly lower systolic blood pressure at 26 weeks compared to sitagliptin. The mean difference was $-4$ mmHg (CI -6 to $-1$ mm of Hg) between once-a-week exenatide and daily sitagliptin. The study did not observe any significant difference on the levels of diastolic blood pressure.\textsuperscript{(32)} Similar to liraglutide, large clinical trials with exenatide have shown a favourable effect on blood pressure.\textsuperscript{(43)} DPP-4 inhibitors, on the other hand have shown variable effects on the blood pressure.\textsuperscript{(44–46)}

The 1860-Lira-DPP-4 study did not observe any significant differences with lipid profile except significant reduction in total cholesterol from baseline with 1.8 mg liraglutide
dose compared to sitagliptin. In the DURATION-2 trial neither exenatide nor sitagliptin produced any significant effect on the lipid profile.

**Hypoglycaemia**

In the DURATION-2 trial there were no reported major hypoglycaemic episodes. Minor hypoglycaemia episode were similar with the exenatide LAR and sitagliptin.\(^{(32)}\)

The 1860-Lira-DPP-4 study reported a single episode of major hypoglycaemia with 1.2 mg liraglutide (blood glucose concentration of 3.6 mmol/l). Minor hypoglycaemia were reported by similar proportions of participants treated with 1.8 mg liraglutide (11 [5%], .370 episodes per participant-year), 1.2 mg liraglutide (12 [5%], .178), and sitagliptin (10 [5%], .106).\(^{(30)}\)

During the extension phase of the 1860-Lira DPP4 study, no episodes of major hypoglycaemia occurred and the minor hypoglycaemia events remained comparable during the whole study period over 52 weeks.\(^{(31)}\)

**Gastrointestinal Side Effects**

As noticed in short term mechanistic studies, all the longer term comparative RCTs showed more initial nausea and vomiting with GLP-1 agonists compared to DPP-4 inhibitors. In the 1860-Lira-DPP-4 study, nausea was more common with liraglutide (21–27%) than with sitagliptin (5%) at the beginning of the therapy but by the end of the trial, symptoms decreased to the level observed with sitagliptin (<3%) and patients reported nausea remained comparable during the extension period.\(^{(30,31)}\) In the DURATION-2 trial nausea was more common with once a week exenatide (24% patients) compared to sitagliptin (10% patients).\(^{(32)}\)
**Incretins and Safety**

Cases of pancreatitis have been reported in patients who were treated with agents in both classes of incretin-based therapies. During the head-to-head comparison trials, no episode of pancreatitis was noticed during the first 26 weeks of the 1860-Lira-DPP4 study. However, an episode of a mild non-acute pancreatitis was reported during the extension period. No cases of pancreatitis were reported during DURATION-2 trial.

Large preclinical studies involving diabetic mice and rats have failed to show an association between GLP-1 agonists like exenatide and liraglutide as well as the DPP-4 inhibitor; sitagliptin and pancreatitis. Large cohort studies looking at healthcare databases have not shown any association with the incretin-based therapies and pancreatitis. A recently published large cohort study, analysed the rates of acute pancreatitis in diabetic subjects treated with exenatide, sitagliptin, and other antidiabetic agents using data from the Medco National Integrated Database from January 2007 to June 2009. The risk of pancreatitis was high in patients with diabetes compared to patients without diabetes (adjusted hazard ratio 2.1 [95% CI 1.7–2.5]), but there was no increased risk of pancreatitis seen in patients treated with exenatide or sitagliptin compared to patients who received other diabetic medications. The available data does not support the association between incretin therapies and pancreatitis. Long-term larger studies are needed to investigate this further. The large on-going outcome trial LEADER (Liraglutide Effects and Actions in Diabetes, Evaluation of Cardiovascular Results) will investigate the safety profile of liraglutide in around 9000 patients with type 2 diabetes. It will include patients with a high risk cardiovascular profile in a global setting. EXSCEL (Exenatide Study of Cardiovascular Event Lowering) is a similar large study planned to investigate the safety of exenatide LAR preparation. EXSCEL is a double-blind randomised, placebo controlled, multinational superiority trial in patients with Type 2 Diabetes. It aims to compare the
impact of including exenatide as part of usual care versus usual care without exenatide on major cardiovascular outcomes. A total of 9,500 patients will be recruited and will be followed for a minimum of 4 years.\(^{(54)}\) TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) will hope to investigate safety and cardiovascular outcomes with sitagliptin. TECOS is a double-blind randomised, placebo-controlled, multinational trial in patients with T2DM. TECOS aims to compare the impact of adding sitagliptin as part of usual care versus usual care without sitagliptin on cardiovascular outcomes. Fourteen thousand patients will be followed for a minimum of 3 years.\(^{(54)}\)

A treatment-related increase in thyroid C-cell proliferative changes has been observed with liraglutide in the lifetime carcinogenicity studies in rats and mice.\(^{(55)}\)

Based on 30 non-clinical mechanistic studies and consistent with the relevant literature it was concluded that the rodent C-cell tumours induced by dosing of liraglutide were caused by a non-genotoxic, specific receptor-mediated mechanism to which rodents are particularly sensitive whereas non-human primates and humans are not.\(^{(55, 56)}\) In line with this, data from long-term clinical studies in more than 5000 patients treated with liraglutide has not shown any increase in the mean calcitonin level which is the marker of C cell hyperplasia.\(^{(57)}\)

**Patient Reported Outcome Measures and Satisfaction**

Diabetes mellitus, its treatment and its complications often affect patient’s quality of life.\(^{(8)}\) Patient reported treatment outcomes may provide the data on health related quality of life as well as may provide information on patients’ perception on efficacy, tolerability and preferences about a particular therapy. Higher patient satisfaction may indicate better compliance with the therapy.\(^{(58–60)}\)
In the 1860-Lira-DPP-4 study group trial, the increase in patients’ treatment satisfaction from baseline was significantly higher with 1.8 mg liraglutide than with sitagliptin \( (n=171) \) vs \( n=170 \); difference 1.39, 95% CI 1.13–2.64), but the increase with 1.2 mg liraglutide versus sitagliptin was not significant. Patients reported significantly greater improvement in treatment satisfaction with liraglutide 1.8 mg than sitagliptin on three items: “current treatment” (difference = .35; \( p = .01 \)), “recommend” (difference = .41; \( p = .003 \)) and “continue” (difference = .44; \( p = .01 \)). Patient perceived themselves less hyperglycaemic on the either doses of liraglutide compared to sitagliptin \( (p<.05) \). There was no difference between liraglutide and sitagliptin on DTSQ items relating to treatment convenience and flexibility, indicating that patients were no less satisfied with the injectable than the oral agent.\(^{(61)}\)

In the DURATION 2 trial weight-related quality of life, psychological general wellbeing, diabetes treatment satisfaction, and general health status were assessed using the Impact of weight related quality of life Lite questionnaire (IWQOL-Lite), Psychological General Well-being (PGWB) index, Diabetes Treatment Satisfaction Questionnaire (DTSQ), and European Quality of life-5 dimension (EQ-5D) at baseline and at week 26. There was no significant difference in all five domains of IWQOL total score between exenatide once a weekly and sitagliptin (IWQOL total score exenatide 5.15, 95% CI 3.11–7.19 and sitagliptin 4.56, 2.56–6.57). A greater improvement in overall treatment satisfaction was recorded with exenatide than with sitagliptin (difference 1.61, 95% CI 0.07 to 3.16, \( p = .0406 \)). However the DURATION 2 was double dummy trial hence all the patients had a tablet as well as an injection hence it’s more difficult to tease out the differences\(^{(32)}\)
CONCLUSIONS

In the clinical trials, both types of incretin based therapies seem to be effective in improving hyperglycaemia, however, as suggested by the proof of concept study, the magnitude of glycaemic improvement was significantly higher with GLP-1R agonists and was consistent in the order of estimated mean treatment difference in HbA1c of .34–.63% over and above that obtained with DPP-4 inhibitors. Greater HbA1c reduction with GLP-1 agonists is probably due to pharmacological concentrations of free (non-albumin-bound) GLP-1 agonists.\(^{(28,62)}\) Compared to 2–3 times increment above baseline in the native GLP concentration achieved using DPP-4 inhibitors, several fold higher levels of GLP-1 agonist leads to greater stimulation of GLP-1 receptor.\(^{(61)}\) Similarly there is also a significantly greater weight loss (estimated mean treatment difference of −1.5 to −2.53 kg) associated with GLP-1 agonists compared to DPP-4 inhibitors. This is most likely due to central satiety effects and effects on the GI system. Although the differences in FPG were not evident during the initial short term proof of concept study, the longer term RCTs have consistently shown greater improvements in FPG with GLP-1 agonists as compared to DPP-4 inhibitors. Sitagliptin has a similar pharmacokinetic half-life to liraglutide (about 12 hour), but the increase in endogenous GLP-1 concentrations with DPP-4 inhibitors occurs mainly after meals. Thus, fasting concentrations of active GLP-1 remain fairly low overnight, so reductions in FPG concentrations with sitagliptin are low compared with liraglutide. Whilst GLP-1 agonists are injected; DPP-4 inhibitors are taken orally and although it is often stated that patients resist injectable therapies, published data suggest this is not by any means a universal finding. The results from 1860 trial with liraglutide suggest patients were no less satisfied with injectable therapy compared to oral DPP-4 inhibitors.\(^{(61)}\)
In general the efficacy and safety of the incretin based agents from both classes have been shown to be durable. The safety with longer term use will be ascertained by currently on-going outcome trials (LEADER, EXSCEL, and TECOS).\(^{(53,54)}\)

Similarly, although the currently marketed DPP-4 inhibitors appear to be comparable as a class regarding the degree of glycaemic improvement, only sitagliptin was tested in these direct head to head comparisons. However sitagliptin is the most widely prescribed DPP-4 inhibitor with license apart from the severe and the end stage renal impairment.

As with the other therapies, the selection of incretin-based agent for glycaemic control in patients with T2DM, should be individualised taking into consideration the aims and intensity of glycaemic improvement, tolerability of the therapy, effect of such therapy on the various co-existing morbidities whilst assuring the therapy is acceptable and safe for patients on the longer term.
List of abbreviations:

DPP-4 inhibitors- dipeptidyl peptidase-4

FDA- Food and Drug Administration

EMA- European Medicine Agency

GLP-1 -Glucagon like peptide 1

IGT- Impaired glucose tolerance

SU- sulphonylureas

T2DM-Type 2 diabetes mellitus

TZD- thiazolidinediones

COMPETING INTERESTS:

KN- The author declares no competing interests.

RK- The author declares no competing interests.

KK- Professor Kamlesh Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. MJD has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk

MD- Professor Melanie Davies has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme and Roche, and as a speaker for Servier. She has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, Glaxo SmithKline and Servier.
Authors' contributions

KN and RK drafted the manuscript.

MD and KK critically reviewed the manuscript
References


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Ref Type: Report


Ref Type: Report


[30] **Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S et al.** 2010 Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate


Ref Type: Online Source


Ref Type: Abstract


Ref Type: Online Source


metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diab Care 32(7):1224–1230.


<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>type</th>
<th>GLP-1 analogue</th>
<th>DPP-4 inhibitor</th>
<th>Co-existing therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeFronzo et al\textsuperscript{28}</td>
<td>4 weeks</td>
<td>Double blind, double dummy, cross over</td>
<td>Exenatide 5mcg twice daily for 1\textsuperscript{st} week followed by 10mcg twice daily for 2\textsuperscript{nd} week</td>
<td>Sitagliptin 100mg once daily</td>
<td>Metformin</td>
</tr>
<tr>
<td>Berg et al\textsuperscript{29}</td>
<td>8 weeks</td>
<td>Double blind, double dummy, cross over</td>
<td>Exenatide 10mcg twice daily</td>
<td>Sitagliptin 100mg once daily</td>
<td>none</td>
</tr>
<tr>
<td>1860-Lira DPP4\textsuperscript{30}</td>
<td>26 weeks</td>
<td>Open label parallel group</td>
<td>Liraglutide 1.2mg and Liraglutide 1.8 mg</td>
<td>Sitagliptin 100mg once daily</td>
<td>Metformin</td>
</tr>
<tr>
<td>DURATION 2\textsuperscript{32}</td>
<td>26 weeks</td>
<td>Double dummy</td>
<td>Exenatide LAR 2mg once weekly</td>
<td>Sitagliptin 100mg once daily</td>
<td>Metformin</td>
</tr>
<tr>
<td>DURATION 4\textsuperscript{33}</td>
<td>26 weeks</td>
<td>Double dummy</td>
<td>Exenatide LAR 2mg once weekly</td>
<td>Sitagliptin 100mg once daily</td>
<td>none</td>
</tr>
<tr>
<td>T-emerge 4\textsuperscript{34}</td>
<td>24 weeks</td>
<td>Double dummy</td>
<td>Taspoglutide 10 mg and 20mg weekly</td>
<td>Sitagliptin 100mg once daily</td>
<td>Metformin</td>
</tr>
<tr>
<td>1860- Lira DPP4 extension\textsuperscript{31}</td>
<td>52 weeks</td>
<td>Open label parallel group</td>
<td>Exenatide 10mcg twice daily</td>
<td>Sitagliptin 100mg once daily</td>
<td>Metformin</td>
</tr>
</tbody>
</table>
Table: 2: Mechanistic differences between GLP-1 agonist exenatide and DPP-4 inhibitor Sitagliptin.

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Exenatide</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in FPG (mmol/l)</td>
<td>1.04 +/- 0.2</td>
<td>0.83 +/- 0.2</td>
<td>P = 0.3234</td>
</tr>
<tr>
<td>Change in PPG (mmol/l)</td>
<td>2.0 +/- 0.3</td>
<td>6.26 +/- 0.3</td>
<td>P &lt; 0.0001*</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>Yes</td>
<td>Yes</td>
<td>P = 0.0239*</td>
</tr>
<tr>
<td>Acute Insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
<td>P = 0.0017*</td>
</tr>
<tr>
<td>Reduction in post-prandial glucagon</td>
<td>Yes</td>
<td>Yes</td>
<td>P = 0.0011*</td>
</tr>
<tr>
<td>Reduction in gastric emptying</td>
<td>none</td>
<td>Yes</td>
<td>P &lt; 0.0001*</td>
</tr>
<tr>
<td>Six point SMBG excursions</td>
<td>Post breakfast</td>
<td>Yes</td>
<td>P = 0.0016*</td>
</tr>
<tr>
<td></td>
<td>Post lunch</td>
<td>Similar to</td>
<td>Post dinner</td>
</tr>
<tr>
<td></td>
<td>Post dinner</td>
<td>Sitagliptin</td>
<td></td>
</tr>
<tr>
<td>Reduction in body weight (Kg)</td>
<td>0.3 +/- 0.2</td>
<td>0.8 +/- 0.2</td>
<td>P = 0.0056*</td>
</tr>
<tr>
<td>Decrement in calorie intake</td>
<td>none</td>
<td>Yes</td>
<td>P = 0.0227*</td>
</tr>
<tr>
<td>Reduction in post-prandial triglyceride levels</td>
<td>yes</td>
<td>Yes</td>
<td>P = 0.018*</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>
### Table: 3

Comparison of GLP-1 analogues in DPP-4 inhibitors- data from fully published RCTs$^{30,31,32}$

<table>
<thead>
<tr>
<th>Study</th>
<th>The 1860- Lira DPP-4 study (52 weeks)</th>
<th>DURATION 2 (26 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8mg/d</td>
<td>Liraglutide 1.2mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin 100mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exenatide LAR 2mg/weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin in 100mg/d</td>
</tr>
<tr>
<td>No of patients</td>
<td>225</td>
<td>221</td>
</tr>
<tr>
<td>Mean baseline HbA1c (%)</td>
<td>8.4 (0.8)</td>
<td>8.4 (0.7)</td>
</tr>
<tr>
<td>Change in HbA1c (%)</td>
<td>-1.51</td>
<td>-1.29</td>
</tr>
<tr>
<td>Mean treatment difference in HbA1c with DPP-4 inhibitor</td>
<td>-0.63 (p &lt; 0.0001)</td>
<td>-0.4 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Mean baseline FPG (mmol/l)</td>
<td>10.1 (2.4)</td>
<td>9.9 (2.4)</td>
</tr>
<tr>
<td>Change in FPG (mmol/l)</td>
<td>-2.04</td>
<td>-1.71</td>
</tr>
<tr>
<td>Mean treatment difference in FPG with DPP-4 inhibitor</td>
<td>-1.45 (p &lt; 0.0001)</td>
<td>-1.13 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Baseline weight (Kg)</td>
<td>93.7 (18.4)</td>
<td>94.6 (18.1)</td>
</tr>
<tr>
<td>Change in weight (Kg)</td>
<td>-3.68</td>
<td>-2.78</td>
</tr>
<tr>
<td>Mean treatment differences in weight with DPP-4 inhibitor</td>
<td>-2.53 (p &lt; 0.0001)</td>
<td>-1.62 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Incidence of hypoglycaemia</td>
<td>0.143 episodes/patient/year</td>
<td>0.154 episodes/patient/year</td>
</tr>
<tr>
<td>Nausea N (%)</td>
<td>60 (27.5)</td>
<td>40 (21.7)</td>
</tr>
<tr>
<td>Diarrhoea N (%)</td>
<td>27 (12.4)</td>
<td>20 (9)</td>
</tr>
</tbody>
</table>