Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus

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INTRODUCTION — Despite advances in options for the treatment of diabetes, optimal glycemic control is often not achieved. Hypoglycemia and weight gain associated with many antidiabetic medications may interfere with the implementation and long-term application of "intensive" therapies [1]. Current treatments have centered on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion.

Glucagon-like peptide-1 (GLP-1)-based therapies (eg, GLP-1 receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake (table 1). These agents do not usually cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia.

This topic will review the mechanism of action and therapeutic utility of GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. DPP-4 inhibitors are discussed separately. A general discussion of the initial management of blood glucose and the management of persistent hyperglycemia in adults with type 2 diabetes is also presented separately. (See "Dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus" and "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

GLUCAGON-LIKE PEPTIDE-1 — Glucose homeostasis is dependent upon a complex interplay of multiple hormones: insulin and amylin, produced by pancreatic beta cells; glucagon, produced by pancreatic alpha cells; and gastrointestinal peptides, including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP; gastric inhibitory polypeptide) (figure 1). Abnormal regulation of these substances may contribute to the clinical presentation of diabetes. The role of GLP-1 in glucose homeostasis is illustrative of the incretin effect, in which oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose [2]. This effect is mediated by several gastrointestinal peptides, particularly GLP-1, that are released in the setting of a meal and stimulate insulin synthesis and insulin secretion, which does not occur when carbohydrate is administered intravenously.

GLP-1 is produced from the proglucagon gene in L-cells of the small intestine and is secreted in response to nutrients (figure 1) [3]. GLP-1 binds to a specific GLP-1 receptor, which is expressed in various tissues, including pancreatic beta cells, pancreatic ducts, gastric mucosa, kidney, lung, heart, skin, immune cells, and the hypothalamus [2,4]. GLP-1 exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets [2]. It has also been shown to slow gastric emptying [5], inhibit inappropriate post-meal glucagon release [3,6], and reduce food intake (table 1) [3]. Owing in part to the effects of GLP-1 on slowed gastric emptying and appetite centers in the brain, therapy with GLP-1 and its receptor agonists is associated with weight loss, even among patients without significant nausea and vomiting. (See 'Weight loss' below.)

In animal models, GLP-1 stimulates beta-cell proliferation and differentiation, preventing diabetes [7,8]. Exenatide, like GLP-1, has been shown to promote beta-cell regeneration and differentiation in prediabetic and diabetic rats [9,10]. Although GLP-1 may hold promise for halting the progression of beta-cell failure that often occurs in type 2 diabetes, the animal model findings have not been replicated in humans. Moreover, after GLP-1 receptor agonists are stopped, their glucose-lowering effectiveness dissipates rapidly, belying their proposed trophic effects on beta cells.

In patients with type 2 diabetes, there is an impaired insulin response to GLP-1, possibly related to a reduction in postprandial GLP-1 secretion (figure 2A-C) [11] or to other mechanisms [12,13]. GLP-1 regulation may also be abnormal in type 1 diabetes [14]. The role of GLP-1 in the treatment of type 1 diabetes is under investigation but is not well defined [15]. We do not currently use GLP-1-based therapies in patients with type 1 diabetes. Therefore, this discussion will be limited to its use in type 2 diabetes. GLP-1 exhibits a short half-life of one to two minutes due to N-terminal degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). This necessitates continuous infusion of GLP-1 to achieve steady-state levels in pharmacologic studies [16]. Research has focused on GLP-1-like agonists that are resistant to DPP-4 degradation and on agents that increase GLP-1 via inhibition of DPP-4.

GLP-1 RECEPTOR AGONISTS — Synthetic glucagon-like peptide-1 (GLP-1) receptor agonists are resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) and therefore have a longer half-life, facilitating clinical use. They bind to the GLP-1 receptor and stimulate glucose-dependent insulin release from the pancreatic islets as described above. They do not usually cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia. (See 'Glucagon-like peptide-1' above.)

Although synthetic GLP-1 receptor agonists improve glycemic control, there are few studies assessing clinically important health outcomes (cardiovascular events, mortality), durability of glucose control or weight loss, or safety.

Glycemic efficacy — GLP-1 receptor agonists are effective in improving glycemic control, as illustrated by the findings of a meta-analysis of 17 randomized trials comparing GLP-1 receptor agonists (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide) with placebo or an active comparator (insulin glargine, DPP-4 inhibitor, thiazolidinedione, sulfonylurea) in patients with type 2 diabetes and suboptimal control on one or two oral agents (metformin and/or sulfonylurea) [17]. The duration of the individual trials ranged from 8 to 30 weeks. In comparison with placebo, all GLP-1 receptor agonists reduced glycated hemoglobin (A1C) by approximately 1 percentage point (treatment difference 0.47 to 1.56 percent).

Although there have been no completed comparative effectiveness studies [18], meta-analysis of the usually short-term (26-week) pharmaceutical company-supported studies has suggested that GLP-1 receptor agonist therapy in patients with baseline A1C levels of 8 to 8.5 percent may lower A1C modestly more (by 0.2 to 0.3 percentage points) than the active comparators [17]. They do so at the expense of substantially higher gastrointestinal side effects and cost. The comparison with other injectable therapy, insulin, is particularly problematic as the intensity of insulin therapy in the comparison group is questionable. In a post-hoc analysis of two 26-week trials comparing insulin with GLP-1 receptor agonists in patients with baseline mean A1C of 8.3 percent, the slightly lower A1C reduction (approximately 0.2 percentage points) with GLP-1 receptor agonists was accompanied by an approximately 3 kg difference in weight at study end, as reported in many studies with GLP-1 receptor agonists, but balanced by a substantial increase in gastrointestinal side effects (14 versus 1 percent) [19]. Moreover, the frequency of major hypoglycemia in the two studies, albeit quite low, was nominally greater in the GLP-1 receptor agonist than in the insulin treatment groups [19]. Future studies comparing these agents with insulin should include dedicated, independent glucose monitoring/insulin titration committees to oversee appropriate insulin titration and vigorously analyze reasons for lack of titration.

The individual drugs and adverse effects are discussed below. (See 'Short-acting GLP-1 receptor agonists' below and 'Long-acting GLP-1 receptor agonists' below and 'Precautions and adverse effects' below.)

Cardiovascular effects — There are several trials assessing clinically important cardiovascular health outcomes in patients taking GLP-1 receptor agonists. Of note, the cardiovascular studies to date (with the possible exception of exenatide) have been carried out in very high-risk populations to increase the hazard rate for major cardiovascular disease (CVD) events and complete the studies in a relatively brief period of time. Therefore, there are few data on CVD safety or putative benefits in lower-risk patients.

In patients with type 2 diabetes and CVD, there was a reduction in CVD outcomes with liraglutide and semaglutide compared with placebo, whereas lixisenatide and exenatide did not increase or decrease CVD outcomes. Liraglutide had no effect on heart failure outcomes in patients with established heart failure.

Differences in CVD outcomes in studies conducted thus far may be related to intrinsic properties of available agents (such as pharmacokinetics and glucose-lowering efficacy) or may be related to differences in patient selection and study design. The trials are reviewed below:

- Liraglutide – In the largest trial, 9340 patients with type 2 diabetes (mean A1C 8.7 percent) and at least one coexisting cardiovascular condition (approximately 80 percent had prior myocardial infarction, stroke, or renal failure) if ≥50 years or at least one cardiovascular risk factor (eg, hypertension, microalbuminuria) if ≥60 years were randomly assigned to liraglutide or placebo [20]. Most patients were on combination therapy, taking either metformin (76 percent), sulfonylureas (50 percent), and/or insulin (44 percent).

  After a median follow-up of 3.8 years, the primary endpoint (time to first occurrence of a composite endpoint [death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke]) occurred in fewer patients in the liraglutide group (13 versus 14.9 percent; hazard ratio [HR] 0.87, 95% CI 0.78-0.97). At 36 months, A1C (mean difference 0.4 percentage points), weight (mean difference 2.3 kg), and systolic blood pressure (mean difference 1.2 mmHg) were lower in the liraglutide group, whereas diastolic blood pressure (mean difference 0.6 mmHg), and heart rate (mean difference 3 beats per minute) were higher in the liraglutide group. There were fewer add-on therapies for diabetes medications, lipid-lowering medications, and diuretics in patients in the liraglutide group than in those in the placebo group. The risk of severe hypoglycemia was lower in the liraglutide group (2.4 versus 3.3 percent).

  In a separate trial of liraglutide versus placebo in 300 patients (59 percent with type 2 diabetes) with established heart failure and reduced left ventricular ejection fraction who were recently hospitalized, liraglutide had no significant effect on the composite outcome (time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level) [21]. In a prespecified subgroup analysis, there was no effect of liraglutide compared with placebo on heart failure outcomes in the subset of patients with diabetes.

- Semaglutide – In the semaglutide trial, 3297 patients with type 2 diabetes (mean A1C 8.7 percent) ≥50 years with established CVD, heart failure, or chronic kidney disease, or age ≥60 years with at least one cardiovascular risk factor, were randomly assigned to semaglutide (0.5 or 1 mg once weekly) or placebo [22]. Most patients were taking combination therapy with either metformin (73 percent), insulin (58 percent), and/or sulfonylureas (43 percent). Cardiovascular medications included antihypertensives (93 percent), lipid-lowering drugs (76 percent), and antithrombotics (76 percent) and were prescribed evenly to both groups.

  After a median follow-up of two years, the primary endpoint (a composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in fewer patients in the semaglutide group (6.6 versus 8.9 percent in the placebo group, HR 0.74, 95% CI 0.58-0.95). Among the individual components of the composite outcome, the occurrence of nonfatal stroke was significantly lower in the semaglutide group (1.6 versus 2.7 percent), whereas the reduction in nonfatal myocardial infarction (2.9 versus 3.9 percent) was not significantly different, and the risk of cardiovascular death (2.7 versus 2.8 percent) was similar. Reductions in A1C (0.7 to 1 percent lower in

the low- and high-dose active treatment groups, respectively, compared with the placebo), systolic blood pressure (1.3 and 2.4 mmHg, respectively), and weight (2.9 and 4.3 kg, respectively) were greater in the semaglutide groups than the placebo group.

Diabetic retinopathy complications occurred more frequently in the semaglutide group. (See 'Microvascular outcomes' below.)

- Lixisenatide – In the lixisenatide trial, 6068 patients with type 2 diabetes and either a myocardial infarction or hospitalization for unstable angina in the past 180 days were randomly assigned to receive lixisenatide or placebo in addition to other diabetes medications (predominantly metformin, insulin, and sulfonylureas) [23]. After a median follow-up of 25 months, the primary endpoint (a composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) occurred in a similar proportion of patients (13.4 and 13.2 percent in the lixisenatide and placebo groups, respectively; HR 1.02, 95% CI 0.89-1.17). There was no significant difference in any of the individual components of the composite endpoint. There was no significant difference in the rate of hospitalization for heart failure (approximately 4 percent in each group). The mean A1C level was approximately 0.27 percentage points lower in the active intervention group than in the placebo group over the course of the study.

- Exenatide **once weekly** – In a noninferiority trial, 14,752 patients with type 2 diabetes (73.1 percent had previous cardiovascular disease) were randomly assigned to receive exenatide or placebo once weekly [24]. After a median follow-up of 3.2 years, the occurrence of the primary endpoint (a composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) did not significantly differ between the two groups (11.4 versus 12.2 percent with placebo, HR 0.91, 95% CI 0.83-1.0). Over the course of the study, the mean A1C level was approximately 0.53 percentage points lower in the exenatide group.

Microvascular outcomes — There are no trials evaluating microvascular disease as the primary outcome in patients taking GLP-1 receptor agonists [25]. In trials designed to assess cardiovascular outcomes in patients with or at high risk for CVD, liraglutide and semaglutide reduced nephropathy outcomes, whereas there was an increase in retinopathy outcomes with semaglutide. The trials are reviewed below:

- Liraglutide – In the liraglutide trial described above (9340 patients with type 2 diabetes and at least one coexisting cardiovascular condition, median follow-up of 3.8 years) [20], the secondary endpoint (a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease) occurred in fewer patients taking liraglutide (5.7 versus 7.2 percent with placebo, HR 0.78, 95% CI 0.67-0.92) [26]. The results were driven by a lower incidence of new-onset persistent macroalbuminuria. There was no significant effect on the incidence of the other three components of the composite outcome.

  There were very few retinal events in this trial.

- Semaglutide – In the semaglutide trial described above (3297 patients with established CVD, heart failure, or chronic kidney disease, or age ≥60 years with at least one cardiovascular risk factor, median follow-up two years), diabetic retinopathy complications occurred more frequently in the semaglutide group (3 versus 1.8 percent in the placebo group, HR 1.76, 95% CI 1.11-2.78), particularly among patients with existing retinopathy, whereas new or worsening nephropathy occurred less frequently (3.8 versus 6.1 percent) [22]. The higher rate of retinopathy complications was unexpected and requires further investigation [27].

- Lixisenatide – In the lixisenatide trial (6068 patients with type 2 diabetes and either a myocardial infarction or hospitalization for unstable angina in the past 180 days, median follow-up 25 months), changes in the urinary albumin-to-creatinine ratio were evaluated [23]. Although the percentage change in the ratio was modestly better with lixisenatide than placebo, the median values at baseline and follow-up were similar in the two groups.

It is important to note these trials were not specifically designed and were of relatively short duration to assess microvascular outcomes. In addition, the presence of baseline retinopathy or neuropathy was not systematically evaluated. Trials with primary microvascular outcomes and in patients who are not at high cardiovascular risk are required in order to better understand the microvascular effects of GLP-1 receptor agonists. The mechanism of these effects also needs to be better understood as the separation in A1C was relatively small and over a relatively brief period of time to affect microvascular disease.

Mortality — The effect of GLP-1 receptor agonists on overall mortality is uncertain. In a systematic review and meta-analysis of 189 trials, there was no difference in all-cause mortality between any incretin drug and control [28]. The results of the meta-analysis were heavily weighted by six large, randomized trials in which 92 percent of all deaths occurred. In a subgroup analysis of the GLP-1 receptor agonist cardiovascular outcomes trials, there was a suggestion of reduced all-cause mortality with GLP-1 receptor agonists versus placebo (7.0 versus 7.8 percent, odds ratio [OR] 0.89, 95% CI 0.80-0.99). Further studies examining the effect of GLP-1 receptor agonists on overall mortality are warranted.

Weight loss — Weight loss is common with GLP-1 receptor agonists. In a systematic review of 17 randomized trials comparing GLP-1 receptor agonists (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide) with placebo or an active comparator (insulin glargine, DPP-4 inhibitor, thiazolidinedione, sulfonylurea) in patients with type 2 diabetes and suboptimal control on one or two oral agents (metformin and/or sulfonylurea), patients randomly assigned to GLP-1 receptor agonists had a weight reduction of approximately 1.5 to 2.5 kg over 30 weeks [17].

The reduction in body weight with GLP-1 receptor agonist treatment was confirmed in another meta-analysis of 21 trials comparing GLP-1 receptor agonists with placebo, no intervention, or other diabetes medications in overweight patients with or without diabetes (weighted mean difference -2.9 kg, 95% CI -3.6 to -2.2) [29]. Weight reduction occurred in patients with (18 trials) and without (three trials) diabetes (mean difference -2.8 and -3.2 kg, respectively). The majority of the trials in the meta-analysis were designed primarily to assess the effect of GLP-1 receptor agonists on glycemic control. Body weight was a secondary endpoint. In addition, there was significant heterogeneity in the results due to differences in trial design. Some of the comparators (sulfonylureas, insulin, thiazolidinediones) cause weight gain, while others (metformin) cause weight loss, and still others (placebo, no intervention, DPP-4 inhibitors) are weight neutral. Subgroup analyses showed a significant but smaller mean change in body weight in the trials in which the control group received placebo (-1.9 kg) and a larger difference when the comparator was insulin (-4.8 kg). Furthermore, weight loss appeared more modest in trials with insulin or sulfonylureas as background therapy, compared with trials with metformin as the sole background. The duration of the individual trials in the meta-analyses ranged from 20 to 52 weeks.

In a subsequent trial designed specifically to evaluate the effect of liraglutide on weight loss in patients with type 2 diabetes, 846 overweight or obese patients (mean weight 106 kg) with type 2 diabetes were randomly assigned to liraglutide (3.0 mg or 1.8 mg once daily) or placebo [30]. All patients were counseled to reduce caloric intake by 500 calories per day and to exercise ≥150 min/week. The majority of patients were treated with metformin only, metformin plus a sulfonylurea, or with diet and exercise alone. After 56 weeks, significant weight loss occurred in the liraglutide groups (-6.4 kg [-6.0 percent] and -5.0 kg [-4.7 percent] compared with -2.2 kg [-2.0 percent] in the placebo group). Treatment with liraglutide was associated with better glycemic control, a reduction in the use of oral hypoglycemic agents, and a reduction in systolic blood pressure. The side effects were similar to those found in previous studies of GLP-1 receptor agonist therapy in diabetes with a three- to sixfold increase in gastrointestinal side effects. Nausea developed in 32.7, 31.4, and 13.7 percent of the participants assigned to 3 mg, 1.8 mg, and placebo, respectively. (See 'Gastrointestinal' below.)

Weight loss may be due, in part, to the effects of GLP-1 on slowed gastric emptying and their well-recognized side effects of nausea and vomiting (see 'Precautions and adverse effects' below). However, slowed gastric emptying is attenuated over time, at least in longer-acting GLP-1 receptor agonists.

The role of GLP-1 as a weight loss agent in patients without diabetes is reviewed separately. (See "Obesity in adults: Drug therapy", section on 'GLP-1 receptor agonists'.)

Candidates — GLP-1 receptor agonists are not considered as initial therapy for the majority of patients with type 2 diabetes [31]. Initial therapy in most patients with type 2 diabetes should begin with diet, weight reduction, exercise, and metformin (in the absence of contraindications). (See "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Choice of initial therapy'.)

After a successful initial response to oral therapy, most patients fail over time and require additional therapy (add a second oral or injectable agent, including insulin, or switch to insulin). For patients who fail initial therapy, there are a number of agents that are available and can be used with metformin. The choice of therapy should be individualized based upon patient characteristics, preferences, and costs. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

GLP-1 receptor agonists may be appropriate to use in combination with metformin (and/or another oral agent) in certain clinical settings, eg, when weight loss or avoidance of hypoglycemia is a primary consideration, the A1C level is close to target (within 1 to 1.5 percentage points), and cost or injection therapy are not major barriers. A prior history of myocardial infarction or stroke might also favor choosing liraglutide as the second drug to be added to metformin. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

GLP-1 receptor agonists generally should not be combined with DPP-4 inhibitors, as there do not appear to be additive effects on glucose lowering [32]. There are limited data to support the use of GLP-1 receptor agonists in combination with prandial insulin [33]. When used in combination with basal insulin, patients using GLP-1 receptor agonists compared with placebo achieved glycemic targets at reduced insulin doses and less hypoglycemia or weight gain but more gastrointestinal side effects [34-36].

Although they improve glycemic control, there are few long-term studies of GLP-1 receptor agonists to assess clinically important health outcomes (cardiovascular events, mortality), durability of glucose control or weight loss, or safety. Many questions remain unanswered regarding clinical use in type 2 diabetes, including long-term benefits and risks and their role in combination with other diabetes medications [37].

Choice of therapy — When a decision has been made to use a GLP-1 receptor agonist, exenatide (two daily injections or one weekly injection), lixisenatide (once-daily injection), liraglutide (once-daily injection), albiglutide (once-weekly injection), dulaglutide (once-weekly injection), or semaglutide (once-weekly injection) are available options.

- We prefer long- over short-acting GLP-1 receptor agonists due to patient convenience. Among the longer-acting agents (liraglutide, exenatide once weekly, albiglutide, dulaglutide, semaglutide), the need for reconstitution, patient preference, and payer coverage are important considerations. Injection procedures are more complicated with once-weekly exenatide or albiglutide compared with liraglutide, dulaglutide, semaglutide, or twice-daily exenatide. Therefore, patient preference is important.

- In the setting of a prior myocardial infarction or stroke, liraglutide or semaglutide should be considered preferentially based on the respective cardiovascular outcomes study results. It is unclear whether the progression of retinopathy seen in the semaglutide study is a direct effect of the drug or a consequence of rapid glycemic control similar to that seen in other settings (see 'Cardiovascular effects' above and 'Microvascular outcomes' above). If semaglutide is prescribed to a patient with a history of diabetic retinopathy, consideration should be given to slower titration to avoid rapid declines in A1C and retinal screening within six months of drug initiation to detect progression of retinopathy (see 'Dosing' below). There are no comparative trials, or for that matter any trials, comparing the effects of different GLP-1 receptor agonists on patient-important, long-term outcomes such as diabetic complications, health-related quality of life, or mortality.

There are a number of comparative trials with glycemia as the primary outcome [38-43]. In trials comparing exenatide administered twice daily with exenatide once weekly, liraglutide once daily, or dulaglutide once weekly, the reduction in A1C with the longer-acting (daily or weekly) GLP-1 receptor agonists was significantly greater (treatment difference -0.3 to -0.7 percent) [38-40,44].

Among the longer-acting GLP-1 receptor agonists, small differences in glucose control favor once-daily liraglutide over exenatide once weekly and albiglutide [41,42]. Glycemic control appears to be similar with liraglutide and dulaglutide [45]. With little data on patient-important outcomes, however, the clinical relevance of the difference in A1C (approximately 0.2 percentage points) in these short-term studies (described below) is unclear. Among the once-weekly GLP-1 receptor agonists (albiglutide, dulaglutide, once-weekly exenatide, taspoglutide), small differences in glucose control may favor dulaglutide and once-weekly exenatide over albiglutide and taspoglutide [46]. However, as there have been no direct comparative effectiveness studies of all four once-weekly agents, any conclusions regarding relative efficacy are speculative.

- In a 26-week trial comparing liraglutide (1.8 mg daily) with exenatide long-acting release (LAR; 2 mg once weekly) in 911 patients who were inadequately controlled (mean A1C approximately 8.4 percent) with oral antihyperglycemic drugs (metformin, sulfonylureas, pioglitazone [monotherapy or in combination]), the reduction in A1C from baseline was greater with liraglutide (-1.48 versus -1.28 percent with exenatide) [41]. Exenatide once weekly did not meet its prespecified non-inferiority margin. The most common side effects, nausea (21 versus 9 percent), diarrhea (13 versus 6 percent), and vomiting (11 versus 4 percent), occurred more frequently in the liraglutide group. Weight loss was slightly greater in the liraglutide group (-3.57 and -2.68 kg).

- In a 32-week trial comparing albiglutide (initial dose 30 mg, titrated to 50 mg once weekly) with liraglutide (initial dose 0.6 mg, titrated to 1.2 and then 1.8 mg daily) in 841 patients with type 2 diabetes inadequately controlled with oral antihyperglycemic drugs, the reduction in A1C from baseline was greater with liraglutide (-0.99 versus -0.78 percentage points with albiglutide) [42]. Albiglutide did not meet its prespecified non-inferiority margin. Gastrointestinal side effects were more common with liraglutide compared with albiglutide (49 versus 36 percent).

- In a 26-week trial comparing dulaglutide (1.5 mg once weekly) with liraglutide (1.8 mg once daily) in 599 patients with type 2 diabetes inadequately controlled with metformin, the reduction in A1C from baseline was similar in the two groups (-1.42 and -1.36 percent, respectively) [45]. Dulaglutide met its prespecified non-inferiority margin. Nausea (20 versus 18 percent), diarrhea (12 versus 12 percent), dyspepsia (8 versus 6 percent), and vomiting (7 versus 8 percent) occurred in a similar proportion of patients in each group.

SHORT-ACTING GLP-1 RECEPTOR AGONISTS — Compared with long-acting glucagon-like peptide-1 (GLP-1) receptor agonists, short-acting GLP-1 receptor agonists (exenatide twice daily and lixisenatide) provide short-lived GLP-1 receptor activation. They tend to have a more pronounced effect on postprandial hyperglycemia and gastric emptying and less effect on fasting glucose [47,48].

Exenatide twice daily — Exendin-4 is a naturally occurring component of the Gila monster (*Heloderma suspectum*) saliva and shares 53 percent sequence identity with GLP-1 [49]. It is resistant to dipeptidyl peptidase-4 (DPP-4) degradation and therefore exhibits a prolonged half-life [50]. Exenatide (half-life 2.4 hours) is synthetic exendin-4. Exenatide exhibits dose-dependent and glucose-dependent augmentation of insulin secretion [51]. Its insulinotropic effects are suppressed as the plasma glucose approaches 4 mmol/L (72 mg/dL). Like GLP-1, exenatide slows gastric emptying, suppresses inappropriately elevated glucagon levels, and leads to weight loss [52,53].

Combination with oral agents — Exenatide reduces A1C levels in patients with type 2 diabetes who are inadequately controlled with other antihyperglycemic agents. As examples:

- A meta-analysis of trials comparing exenatide (5 or 10 mcg twice daily) versus placebo in patients suboptimally controlled on maximally effective or tolerated doses of sulfonylurea, metformin, combination

of sulfonylurea and metformin, or thiazolidinedione therapy (alone or with metformin) reported a greater decline from baseline A1C values in the exenatide group compared with placebo (for 10 mcg twice daily, weighted mean difference in change in A1C -0.97 percent, 95% CI -1.16 to -0.79) [54].

Although all of these studies were less than 30 weeks in duration, open-label extension studies have demonstrated sustained lowering of A1C at two years [55,56]. Of note, the open-label extension studies suffer from a "survivor effect," such that only those subjects who remain on the drug are usually included. Thus, these long-term results tend to provide an exaggerated benefit compared with average use.

- In two randomized, open-label trials comparing exenatide with insulin glargine or biphasic insulin aspart in patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea, there were similar reductions in A1C in the exenatide and insulin groups (approximately -1.0 percentage points) [57,58]. The exenatide groups exhibited weight loss as opposed to weight gain and improved postprandial glucose control compared with either insulin group and less nocturnal hypoglycemia compared with insulin glargine.

  In the glargine comparison study, insulin was titrated based upon achieving a target fasting glucose level <100 mg/dL (5.6 mmol/L). The target level was reached in only 21.6 percent of the subjects randomly assigned to glargine, and the average dose used (25 units) was substantially lower than in most studies. The relatively unaggressive insulin therapy may have balanced overall glycemic control in favor of exenatide, though nocturnal hypoglycemia may have played a role (0.9 versus 2.4 events/patient-year). Overall rates of symptomatic hypoglycemia were otherwise similar.

- In a randomized, open-label trial comparing exenatide with glimepiride in 1029 patients with type 2 diabetes taking metformin (mean baseline A1C 7.5 percent), short-term treatment failure (defined as A1C >9 percent after the first three months of treatment or >7 percent at two consecutive visits after the first six months) occurred less often in the exenatide group (41 versus 54 percent, hazard ratio [HR] 0.75, 95% CI 0.62-0.90) [59]. The median time to treatment failure was 180 and 142 weeks for exenatide and glimepiride, respectively. However, at three years, mean A1C values in the 397 patients who were not discontinued from the study due to treatment failure or who did not drop out voluntarily were similar (approximately 7.3 and 7.1 percent in the glimepiride and exenatide groups, respectively). Of note, the average dose of glimepiride used in the study (2 mg daily) was lower than the usual dose (3 to 4 mg) in most studies.

Combination with basal insulin — The combination of exenatide and insulin has been evaluated in clinical trials [60-62]. In a placebo-controlled trial, exenatide added to appropriately titrated insulin glargine reduced A1C by approximately 0.7 percentage points [60]. Participants receiving twice-daily exenatide were more likely to attain goal A1C of <7 percent (60 versus 35 percent in placebo) without an increase in hypoglycemia rates, with the predominant glucose-lowering effect on postprandial hyperglycemia. Twice-daily exenatide was associated with an average weight loss of 1.8 kg compared with an average weight gain of 1.0 kg in the placebo group. The group receiving twice-daily exenatide was more likely to report gastrointestinal symptoms (nausea, diarrhea, and emesis).

Exenatide should not be substituted for basal insulin, as illustrated by the results of a randomized trial that examined replacement of insulin with exenatide in patients with type 2 diabetes treated with combination insulin and oral agents [63]. Glycemic control deteriorated in 38 percent (11 of 29 patients) when exenatide was substituted, compared with 19 percent (3 of 16 patients) who continued insulin. Patients who lost glycemic control were more likely to have a longer duration of disease, lower C-peptide concentrations (suggesting less endogenous beta-cell function), and larger insulin requirements at baseline.

Dosing — Exenatide is available in many countries for the treatment of type 2 diabetes as monotherapy or in combination with oral agents or insulin glargine [64,65]. Exenatide, packaged in prefilled syringes that hold a month's supply of either 5 or 10 mcg doses, is administered subcutaneously twice daily immediately before or within one hour before the morning and evening meals [66]. Exenatide should not be used in

patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage kidney disease [67]. Caution is suggested in prescribing for patients with confirmed gastroparesis. (See 'Precautions and adverse effects' below.)

Lixisenatide — Lixisenatide is a GLP-1 receptor agonist that shares some structural elements with exendin-4 [68]. Compared with native GLP-1, it has a prolonged half-life (2.7 to 4.3 hours); however, its half-life is shorter than that of liraglutide and the other longer-acting GLP-1 receptor agonists. (See 'Long-acting GLP-1 receptor agonists' below.)

Lixisenatide is available in Europe, Japan, and in the United States for use in combination with oral agents or basal insulin in adults with inadequately controlled type 2 diabetes [69]. It is not considered a first-line therapy.

Combination with oral agents — Lixisenatide has been studied as monotherapy and in combination with one or two oral agents (metformin, pioglitazone, sulfonylureas) [70-76]. As examples:

- In a 24-week, double-blind trial of lixisenatide (20 mcg once daily in the morning or evening) versus placebo in 680 patients with type 2 diabetes inadequately controlled with metformin (mean A1C 8.1 percent), the mean reduction in A1C was significantly greater with lixisenatide (-0.9 versus -0.4 percent with placebo) [72].

- In a 24-week, noninferiority trial of once-daily, subcutaneous lixisenatide (20 mcg once daily) versus exenatide (10 mcg twice daily) in 634 patients with type 2 diabetes inadequately controlled with metformin alone (mean baseline A1C 8 percent), lixisenatide was noninferior to exenatide (mean change A1C -0.79 versus -0.96 percent with exenatide) [70].

Combination with basal insulin — Lixisenatide has been evaluated for use in combination with basal insulin therapy [77-79]. As an example, in a 24-week, double-blind trial, 495 patients with type 2 diabetes inadequately controlled with insulin glargine and metformin (mean A1C 8.4 percent) were randomly assigned to the addition of lixisenatide or placebo [78]. The reduction in A1C was significantly greater in the lixisenatide group (-0.6 versus -0.3 percent).

Dosing — Lixisenatide is available in a prefilled pen containing 14 doses of either 10 or 20 mcg of lixisenatide. It should be stored in the refrigerator. The initial dose is 10 mcg subcutaneously once daily, administered within one hour prior to any meal of the day [80]. After two weeks, the dose can be increased to 20 mcg once daily. It can be injected in the thigh, abdomen, or upper arm.

If lixisenatide is added to existing sulfonylurea or basal insulin therapy, a reduction in the dose of these medications may be necessary to prevent hypoglycemia. Lixisenatide is not recommended for use in patients with renal impairment and estimated glomerular filtration rate (eGFR) <30 mL/min. (See 'Precautions' below.)

LONG-ACTING GLP-1 RECEPTOR AGONISTS — Glucagon-like peptide-1 (GLP-1) receptor agonists with greater resistance to dipeptidyl peptidase-4 (DPP-4) degradation have been developed. These agents activate the GLP-1 receptor continuously at their recommended dose and have a prolonged half-life, allowing for once-daily or once-weekly subcutaneous injection. Compared with short-acting GLP-1 receptor agonists, longer-acting GLP-1 receptor agonists tend to have a more marked effect on fasting glucose and less effect on gastric emptying and postprandial glucose [47].

Liraglutide (once daily), extended release exenatide (once weekly), albiglutide (once weekly), dulaglutide (once weekly), and semaglutide (once weekly) are long-acting GLP-1 receptor agonists available in the United States, Europe, and Japan (liraglutide and exenatide) [81,82]. When a decision has been made to use a GLP-1 receptor agonist, we prefer long- over shorter-acting GLP-1 receptor agonists due to patient convenience. Among long-acting agents, patient preference and payer coverage are important considerations. Comparative trials with glycemia as the primary outcome are reviewed above. (See 'Choice of therapy' above.)

Liraglutide — Liraglutide is a GLP-1 receptor agonist that has been modified to noncovalently bind to serum albumin through a lipid side chain, resulting in slower degradation (half-life 11 to 15 hours) and allowing for once-daily, subcutaneous dosing [83]. The efficacy of liraglutide monotherapy was demonstrated in the following studies:

- In a dose-response study of liraglutide monotherapy versus placebo in 165 patients with type 2 diabetes, the proportion of patients achieving a A1C of ≤7 percent was 46, 48, 38, and 5 percent for the three doses of liraglutide (1.90, 1.25, 0.65 mg) and placebo, respectively [84].

- In a 52-week trial of monotherapy with liraglutide (1.2 or 1.8 mg) versus glimepiride (8 mg) in 746 patients with recently diagnosed type 2 diabetes, the proportions of patients achieving an A1C of ≤7 percent were 43, 51, and 28 percent, respectively. Reductions in A1C were significantly greater with liraglutide 1.2 and 1.8 mg (0.84 and 1.14 percentage points versus 0.51 with glimepiride) [85]. In addition, the A1C reduction with 1.8 mg of liraglutide was greater than that with 1.2 mg.

Combination with oral agents — Liraglutide is also effective when used in combination with one (metformin [86,87], sulfonylureas [88,89]) or two (sulfonylurea plus metformin [90], thiazolidinediones plus metformin [91]) oral agents. As examples:

- In a 26-week, randomized trial of once-daily, subcutaneous liraglutide (0.6, 1.2, or 1.8 mg), glimepiride (4 mg daily), or placebo in 1091 patients with type 2 diabetes treated with metformin, reductions in A1C (approximately 1 percentage point) were significantly greater with liraglutide or glimepiride [86]. Mean A1C values did not differ between the liraglutide (1.2 and 1.8 mg) and glimepiride groups.

- In a 26-week, randomized trial of once-daily, subcutaneous liraglutide (1.2 or 1.8 mg) versus oral sitagliptin (100 mg) in 665 patients with type 2 diabetes inadequately controlled with metformin alone (mean baseline A1C 8.5 percent), the mean reduction in A1C was significantly greater with either dose of liraglutide (-1.24 and -1.50 compared with -0.90 percentage points with sitagliptin) [87].

Combination with basal insulin — Liraglutide has been evaluated for use in combination with basal insulin therapy.

- In a 26-week, open-label trial of insulin detemir versus no insulin treatment in 988 patients with type 2 diabetes and A1C >7 percent on combination metformin and liraglutide (1.8 mg daily), the reduction in A1C was significantly greater in the insulin group (treatment difference -0.52 percentage points) [92]. The combination of liraglutide, detemir, and metformin resulted in an average 0.16 kg weight decrease at study conclusion. Rates of nonsevere, biochemical hypoglycemia (blood glucose <55 mg/dL [<3.1 mmol/L]) were more common in those on insulin compared with those who were not (9.2 versus 1.3 percent), with no significant differences in more severe hypoglycemia.

- In a 26-week, double-blind trial, 413 patients with type 2 diabetes inadequately controlled with basal insulin and metformin were randomly assigned to replace the basal insulin with insulin degludec or insulin degludec plus liraglutide; all patients continued metformin [93]. The reduction in A1C was significantly greater in the degludec-liraglutide group (treatment difference -1.1 percentage point). The mean reduction in weight with degludec-liraglutide was 2.7 kg versus no change with degludec alone. The incidence of hypoglycemia was similar. The interpretation of these results is unclear as the dose of insulin in the degludec only and degludec-liraglutide combination was limited to 50 units.

- In a 26-week, open-label trial, 557 patients with type 2 diabetes inadequately controlled with metformin plus glargine were randomly assigned to glargine titration or degludec plus liraglutide coformulation [36]. The reduction in A1C was greater in the degludec-liraglutide group (-1.81 versus -1.13 percentage points with glargine). Patients receiving degludec-liraglutide lost weight (-1.4 kg versus +1.8 kg gain with insulin). There were fewer hypoglycemic events per patient-year in the degludec-liraglutide group compared with the glargine group (2.23 versus 5.05). In this study, degludec could be titrated to a maximum dose of 50 units per day, while there was no maximum dose of glargine. At study end, the

mean daily dose of degludec-liraglutide was 41 dose steps (41 units of degludec plus 1.48 mg of liraglutide), compared with 66 units of glargine.

Dosing — Liraglutide is available for use as monotherapy as an adjunct to diet and exercise or in combination with oral agents and basal insulin in adults with type 2 diabetes. It is not considered a first-line therapy. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

Liraglutide is available in prefilled pens. The initial dose is 0.6 mg once daily for one week to reduce gastrointestinal side effects [94]. After one week, the dose should be increased to 1.2 mg once daily for one week. If blood glucoses remain above the goal range, the dose can be increased to 1.8 mg once daily. (See 'Precautions and adverse effects' below.)

Exenatide once weekly — A sustained-release formulation of subcutaneous exenatide, exenatide once weekly (median half-life of two weeks) reduces A1C levels in patients with type 2 diabetes who are inadequately controlled with metformin and/or diet and exercise [95-97].

Combination with oral agents — Exenatide once weekly has been studied in comparison with twice-daily exenatide, insulin glargine, glimepiride, sitagliptin, pioglitazone, and dapagliflozin [40,59,96-98]. Exenatide once weekly decreased A1C by approximately 1.5 to 1.6 percentage points compared with reductions of 0.9 (sitagliptin and twice daily exenatide) to 1.4 percentage points for the comparators.

In a trial comparing the addition of exenatide once weekly (2.0 mg) or insulin glargine (once daily) with oral agents (metformin with or without sulfonylurea) in 456 adults with type 2 diabetes, the following results were noted [96]:

- The mean reduction in A1C at 26 weeks was slightly but significantly greater in the exenatide once weekly group (-1.5 versus -1.3 percentage points with glargine). The clinical importance of the small difference in A1C is uncertain. In addition, it is unclear if insulin glargine was adequately titrated since only 21 percent of patients taking insulin glargine had fasting glucose levels within the goal range (72 to 99 mg/dL [4.0 to 5.5 mmol/L]). It is unclear whether hypoglycemia, which was more common in the glargine group (26 versus 8 percent), may have contributed to suboptimal insulin dose titration.
- Weight loss occurred more frequently in patients treated with exenatide once weekly versus glargine (-2.6 versus +1.4 kg).
- More patients discontinued exenatide once weekly than glargine due to nausea and injection site reactions, which occurred in 13 percent of patients in the exenatide group compared with 1 to 2 percent in the glargine group. Pancreatitis occurred in one patient treated with exenatide once weekly. (See 'Precautions and adverse effects' below.)

Dosing — The extended-release form of exenatide is available for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes [99]. It is not considered a first-line therapy. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

The dose is 2 mg subcutaneously once weekly, at any time of day and with or without meals. It can be administered in the abdomen, thigh, or upper arm on a rotating basis. Exenatide once weekly is available in two different formulations, either of which should be stored in the refrigerator (36 to 46°F [2 to 8°C]). One formulation is a single-dose plastic tray (containing a syringe with diluent, a vial of lyophilized medication, a vial connector to ease mixing of the medication with the diluent, and a needle for injecting). The other formulation is a single-dose pen. With either formulation, the medication in powder form must be mixed with a diluent. Once mixed, it must be injected immediately. It cannot be stored for injection at a later time. (See 'Precautions and adverse effects' below.)

Albiglutide — Albiglutide is a long-acting GLP-1 receptor agonist generated by the fusion of a DPP-4-resistant GLP-1 dimer to human albumin [100]. The half-life of albiglutide is five to seven days, which allows for once-weekly administration. It is available for use in the United States and Europe as monotherapy (in addition to diet and exercise) or in combination with metformin, glimepiride, pioglitazone, or basal insulin in adults with type 2 diabetes [81,82]. It is not considered a first-line therapy.

Combination with oral agents — Albiglutide has been studied as monotherapy and in combination with one or two oral agents (metformin, pioglitazone, sulfonylureas) [101-105]. As examples:

- In a one-year trial of albiglutide versus insulin glargine in 779 patients with type 2 diabetes inadequately controlled with metformin (with or without a sulfonylurea), the mean A1C reduced from 8.28 to 7.62 percent in the albiglutide group and from 8.36 to 7.55 percent in the glargine group [104]. Albiglutide met its prespecified non-inferiority margin. Glargine was significantly more effective than albiglutide in reducing fasting blood glucose (mean reduction 37.1 versus 15.7 mg/dL [2.06 versus 0.87 mmol/L]). However, the dose of glargine was not aggressively or systematically uptitrated based upon glucose measurements. The mean dose of glargine increased from 10 units daily at baseline to 35 units daily. In the albiglutide group, 67 percent of patients increased the dose from 30 to 50 mg weekly.

  Symptomatic hypoglycemia occurred in 18 percent of patients taking albiglutide compared with 27 percent taking glargine; thus, it is possible that hypoglycemia may have limited dose titration. However, the incidence of severe hypoglycemia (requiring assistance from others) was the same in both groups (0.4 percent). The albiglutide group exhibited weight loss (-1.1 kg) as opposed to weight gain in the insulin group (+1.6 kg). Overall, there were more treatment-related adverse events in the albiglutide group, and more albiglutide- than insulin-treated patients withdrew because of an adverse event (6.9 versus 2.5 percent). (See 'Adverse effects' below.)

- In a two-year trial of weekly albiglutide versus daily sitagliptin, daily glimepiride, and weekly placebo in patients with type 2 diabetes inadequately controlled with metformin (mean A1C 9.1 to 8.2 percent), the reduction in A1C from baseline among the four groups was -0.6, -0.3, -0.4, and +0.3 percentage points, respectively [101]. Although statistically significant, the mean reduction in A1C from baseline in the albiglutide group compared with the sitagliptin and glimepiride groups was small and of uncertain clinical relevance.

- In a 52-week trial of pioglitazone, albiglutide, or placebo in 685 patients inadequately controlled with metformin and glimepiride, the reduction in A1C was greater with pioglitazone (-0.8 versus -0.55 percentage points with albiglutide) [105]. Albiglutide did not meet its prespecified noninferiority margin compared with pioglitazone. Although pioglitazone more effectively reduced A1C, it was associated with a greater increase in weight (+4.4, -0.4, and -0.4 kg with pioglitazone, albiglutide, and placebo, respectively) and a higher incidence of confirmed hypoglycemia (25, 14, and 14 percent, respectively). Overall, there were more treatment-related adverse events in the albiglutide group (gastrointestinal, injection site reactions). (See 'Adverse effects' below.)

Combination with basal insulin — Albiglutide has also been used in combination with basal insulin. As an example:

- In a 26-week trial of once-weekly albiglutide versus three-times-daily prandial insulin lispro in 586 patients with type 2 diabetes inadequately controlled with insulin glargine and metformin, mean A1C reduced from 8.5 to 7.7 percent with albiglutide and from 8.4 to 7.8 percent with lispro [106]. Albiglutide met its prespecified noninferiority margin.

  After eight weeks, the dose of albiglutide was uptitrated to 50 mg weekly based upon a prespecified A1C (>8 percent) in 51 percent of patients. Although there was an insulin titration scheme based upon self-monitored fasting (goal <100 mg/dL [5.6 mmol/L]) and pre- and postprandial glucose data, a limitation of this study is that the titration scheme was followed at the discretion of the investigators. The mean fasting glucose at 26 weeks was above 135 mg/dL (7.5 mmol/L) in both groups, exceeding the titration

goal of <100 mg/dL. The dose of glargine was 53.2 and 50.6 units in the albiglutide and lispro groups, respectively: an increase of only 6 to 7 units over 26 weeks. The mean lispro dose increased from 15.5 to 30.6 units daily during the trial. Pre- and postprandial glucose values were not reported, and therefore, it is unclear if the lispro insulin was optimally titrated. As a result, the comparisons between albiglutide and lispro should be interpreted with caution. The relatively higher frequency of symptomatic hypoglycemia in the lispro arm compared with albiglutide (29.9 versus 15.8 percent) may have been a limiting factor in optimal insulin-dose titration.

Dosing — Albiglutide is available in prefilled pens that contain a powder (30 or 50 mg) and a diluent to make a solution that is injected subcutaneously (abdomen, thigh, or upper arm) once weekly. The initial dose is 30 mg. If, after six to eight weeks, blood glucoses remain above the goal range, the dose can be increased to 50 mg once weekly. (See 'Precautions and adverse effects' below.)

Dulaglutide — Dulaglutide is a long-acting GLP-1 receptor agonist with structural modifications to prevent degradation by DPP-4 and to prolong its half-life. The half-life of dulaglutide is approximately five days, which allows for once-weekly administration. It is available for use in the United States and Europe as monotherapy (in addition to diet and exercise) or in combination with metformin, sulfonylureas, and pioglitazone in adults with type 2 diabetes [107,108]. It is not considered a first-line therapy.

Combination with oral agents — Dulaglutide has been studied as monotherapy and in combination with one or two oral agents (metformin, pioglitazone, sulfonylureas) [44,109-112]. As an example:

- In a 52-week trial of weekly dulaglutide (0.75 or 1.5 mg weekly) versus sitagliptin in 1098 patients with type 2 diabetes inadequately controlled with metformin, the reduction in mean A1C was significantly greater with either dose of dulaglutide (mean A1C reduced from 8.2 to 7.3 percent with dulaglutide 0.75 mg weekly, from 8.1 to 7.0 percent with dulaglutide 1.5 mg weekly, and from 8 to 7.6 percent with sitagliptin) [111]. The mean change in body weight was significantly better with dulaglutide (-2.6 and -3 kg versus -1.53 kg with sitagliptin).

Combination with prandial insulin — Dulaglutide has also been studied in combination with prandial insulin. As an example, in a 52-week, open-label trial of weekly dulaglutide (1.5 or 0.75 mg) or daily bedtime glargine in 884 patients with type 2 diabetes treated with prandial insulin lispro with or without metformin, the reduction in A1C at 26 weeks was greater with high- or low-dose dulaglutide than with glargine (-1.48 and -1.42 versus -1.23 percentage points) [33]. The adjusted mean difference versus glargine (-0.22 and -0.17 percentage points for high- and low-dose dulaglutide, respectively) was statistically significant but not likely clinically significant.

The proportion of patients achieving an A1C <7 percent was 59 and 49 percent for dulaglutide 1.5 mg and glargine, respectively. Insulin lispro doses were approximately 30 percent higher in the dulaglutide groups (88 and 95 versus 69 units for those randomized to glargine). At 52 weeks, mean weight remained relatively stable in the dulaglutide 1.5 mg group and increased in the dulaglutide 0.75 mg and glargine groups (approximately 1.5 and 3.5 kg, respectively). The incidence of nocturnal hypoglycemia <54 mg/dL (<3.0 mmol/L) was significantly lower in the dulaglutide 1.5 mg group than in the glargine group (33 versus 44 percent), with no difference in the incidence of total or severe hypoglycemia among the three groups. Nausea, vomiting, and diarrhea were three- to eightfold times more common with dulaglutide than with glargine.

Dosing — Dulaglutide is available in a ready-mixed pen or prefilled syringe and is injected subcutaneously in the abdomen, thigh, or upper arm once weekly. Dulaglutide should be stored in the refrigerator. However, if needed, each single-dose pen or prefilled syringe can be kept at room temperature for a total of 14 days. The initial dose is 0.75 mg once weekly. If, after six to eight weeks, blood glucoses remain above the goal range, the dose can be increased to 1.5 mg once weekly.

Semaglutide — Semaglutide is a long-acting GLP-1 receptor agonist (94 percent homology with native human GLP-1) with structural modifications to reduce renal clearance and decrease degradation by DPP-4,

resulting in slower degradation (half-life 155 to 184 hours) and allowing for once-weekly subcutaneous, or potentially once-daily oral, dosing [113-116]. Semaglutide is the only GLP-1 receptor agonist that has shown to be effective when given orally [114], although only the subcutaneous preparation is currently available in the United States and Europe as an adjunct to diet and exercise in adults with type 2 diabetes. It is not considered a first-line therapy.

The efficacy of semaglutide monotherapy in lowering glycemia was demonstrated in the following studies:

- In a 30-week trial comparing once-weekly subcutaneous semaglutide (0.5 or 1 mg) and placebo in 388 patients with type 2 diabetes treated with diet and exercise alone (mean A1C 8.05 percent), the reduction in A1C was greater with semaglutide (-1.45 and -1.55, respectively, compared with -0.02 percentage points with placebo) [117].

- In a 30-week trial comparing once-weekly subcutaneous semaglutide (0.5 or 1 mg) and once-daily oral sitagliptin (100 mg) in 308 Japanese patients with type 2 diabetes, previously treated with diet and exercise or oral agent monotherapy, the reduction in A1C was greater with semaglutide (-1.9 and -2.2 percentage points, respectively, versus -0.7 percentage points with sitagliptin) [118]. A higher proportion of patients discontinued treatment for adverse events in the semaglutide 1 mg group (10.8 percent compared with 2.9 percent with semaglutide 0.5 mg and 1.9 percent with sitagliptin).

- In a 26-week trial comparing once-daily **oral** semaglutide (several doses) with once-weekly subcutaneous semaglutide (1 mg) or oral placebo in 632 patients with type 2 diabetes (mean A1C 7.9 percent), the reduction in A1C was greater with oral and subcutaneous semaglutide (-0.7 to -1.9 [dose dependent] and -1.9 percentage points, respectively, compared with -0.3 percentage points with placebo) [114]. Adverse effects of oral and subcutaneous semaglutide were similar. (See 'Precautions and adverse effects' below.)

Combination with oral agents — Semaglutide has also been evaluated in combination with oral agents. As examples:

- In a 30-week, randomized trial of once-daily, subcutaneous semaglutide (0.5 or 1 mg) versus insulin glargine in 1029 patients with type 2 diabetes inadequately controlled with metformin and/or sulfonylurea (mean baseline A1C 8.17 percent), the mean reduction in A1C was significantly greater with either dose of semaglutide (-1.21 and -1.64 compared with -0.83 percentage points with insulin glargine) [119]. However, it is unclear if insulin glargine was adequately titrated.

- In a 56-week, randomized trial of once-daily, subcutaneous semaglutide (0.5 or 1 mg) versus oral sitagliptin (100 mg) in 1231 patients with type 2 diabetes inadequately controlled with metformin, thiazolidinediones, or both (mean baseline A1C 8.1 percent), the mean reduction in A1C was significantly greater with either dose of semaglutide (-1.3 and -1.6 compared with -0.5 percentage points with sitagliptin) [120].

Dosing — Semaglutide is available in single-use, prefilled pens that deliver 0.25/0.5 mg per injection or 1 mg per injection. The initial dose is 0.25 mg by subcutaneous injection (abdomen, thigh, or upper arm) once weekly for four weeks. After four weeks, the dose is increased to 0.5 mg once weekly [121]. If blood glucoses remain above the goal range after at least four weeks on 0.5 mg weekly, the dose can be increased to 1 mg weekly. No dose adjustment is required in patients with renal or hepatic impairment.

In the semaglutide trial described above (in patients with established CVD, heart failure, or chronic kidney disease), diabetic retinopathy complications occurred more frequently in the semaglutide group, particularly among patients with existing retinopathy (see 'Microvascular outcomes' above). Therefore, for patients with a history of diabetic retinopathy who are initiating semaglutide, consideration should be given to slower titration to avoid rapid declines in A1C and retinal screening within six months of drug initiation to detect progression of retinopathy.

PRECAUTIONS AND ADVERSE EFFECTS

Precautions — GLP-1 receptor agonists should not be used in patients with a history of pancreatitis. In addition, GLP-1 receptor agonists are not approved by the US Food and Drug Administration (FDA) for use in those with type 1 diabetes. Many of the salutary effects of these agents are independent of islet-cell function (insulin sensitivity, decreased glucagon, weight loss) and might benefit specific individuals with type 1 diabetes. In exploratory studies of GLP-1 receptor agonists in combination with insulin therapy in patients with type 1 diabetes, there was clinical improvement in glycemic control with a decrease in daily insulin requirement and weight loss [15,122-124]. Until additional data are available, however, we do not use GLP-1 receptor agonists in patients with type 1 diabetes.

Exenatide (twice-daily and once-weekly formulations) and lixisenatide should not be used in patients with:

- Estimated glomerular filtration rate (eGFR) <30 mL/min
- Severe gastrointestinal disease (eg, gastroparesis)

Liraglutide, albiglutide, dulaglutide, exenatide once weekly, and semaglutide should not be used in patients with:

- A personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B

Liraglutide, albiglutide, and dulaglutide should be used with caution in patients with renal impairment.

Adverse effects — The side effects of GLP-1 receptor agonists are predominantly gastrointestinal, particularly nausea, vomiting, and diarrhea, and occur consistently in trials in 10 to 50 percent of patients [17]. The risk of hypoglycemia is small. Hypoglycemic events may occur, however, when GLP-1 receptor agonists are given in conjunction with diabetes medications known to cause hypoglycemia (eg, basal insulin, sulfonylureas, glinides). For the majority of patients in whom the addition of GLP-1 receptor agonists is prompted by poor glycemic control, a reduction in the dose of basal insulin, sulfonylureas, and glinides is not typically necessary, although all patients should be informed of the possibility of hypoglycemia.

The long-term safety of GLP-1 receptor agonists has not been established.

Gastrointestinal — In a meta-analysis of 17 randomized trials comparing GLP-1 receptor agonists (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide) with placebo or an active comparator (insulin glargine, dipeptidyl peptidase-4 [DPP-4] inhibitor, thiazolidinedione, sulfonylurea) in patients with type 2 diabetes and suboptimal control on one or two oral agents, patients randomly assigned to treatment with GLP-1 receptor agonists compared with placebo or active comparator experienced more nausea (8 to 40 percent more), diarrhea (3 to 118 percent more), and weight loss (-1.3 to -5.1 kg) [17].

Nausea may wane with duration of therapy and can be reduced with dose titration [125]. Nausea is the most frequent adverse event with exenatide once weekly, but it has been reported less frequently with once-weekly than with twice-daily administration (26 versus 50 percent) and also less frequently than with liraglutide (9 versus 21 percent) [40,41].

These agents are associated with decreased gastric transit and must be used with caution in those with gastroparesis.

Pancreas — Acute pancreatitis has been reported in association with GLP-1 agonist treatment. At the current time, there are insufficient data to know if there is a causal relationship. Pancreatitis should be considered in patients with persistent severe abdominal pain (with or without nausea), and GLP-1 receptor agonists should be discontinued in such patients. If pancreatitis is confirmed, it should not be restarted. In addition, GLP-1 receptor agonists should not be initiated in a patient with a history of pancreatitis.

Postmarketing reports of acute pancreatitis (including cases of necrotizing or hemorrhagic pancreatitis and fatalities) in patients taking exenatide were submitted via the MedWatch system soon after its introduction

[126-128]. In five liraglutide trials including over 3900 patients, there were seven cases of pancreatitis in patients randomly assigned to liraglutide and one case in a patient using another diabetes drug [129]. Furthermore, in a population-based case-control study using a large insurance database, treatment with GLP-1-based therapy (sitagliptin and exenatide) was associated with an increased risk of hospitalization for acute pancreatitis (adjusted odds ratio [OR] 2.07, 95% CI 1.36-3.13) [130]. In contrast, retrospective cohort studies [131-133] and meta-analyses of randomized trials [134,135] did not identify an increased risk. In population-based cohort studies, there was no difference in the risk of pancreatitis in patients taking GLP-1-based therapies compared with sulfonylureas (1.45 and 1.47 per 1000 patients per year, respectively) [136] or other oral agents [137]. Overall, the incidence of pancreatitis is low (16 cases among 14,562 patients enrolled in GLP-1 agonist randomized trials) [135].

There have also been reports of an increased risk of subclinical pancreatic inflammation, pancreatic cancer, and neuroendocrine tumors in exenatide users [128,138-140]. A causal relationship has not been established. After a review of currently available data, the FDA and the European Medicines Agency agreed that there was insufficient evidence to confirm an increased risk of pancreatic cancer with use of GLP-1-based therapies [141-143]. However, concerns remain [144], and monitoring for and reporting of pancreatic adverse effects will continue [141,143,145].

Injection site reactions — In studies comparing insulin administration with once-weekly GLP-1 receptor agonists, including albiglutide and exenatide, local site reactions are more common with GLP-1 receptor agonists (approximately 10 percent), compared with 1 to 5 percent with insulin [104,106]. In comparison trials, injection site reactions were significantly more common with exenatide once weekly compared with exenatide twice daily [38] and more common with exenatide once weekly [41] or albiglutide [42] than liraglutide. Reactions noted with exenatide once weekly include abscess, cellulitis, and necrosis, with or without subcutaneous nodules [146].

Immunogenicity — Antibodies to GLP-1 receptor agonists may develop. In the majority of patients, the titer of antibodies decreases over time and does not affect glycemic control. However, some patients develop high titers of antibodies that may attenuate the glycemic response [147]. In a meta-analysis of 17 trials, the proportion of patients with antibodies against GLP-1 was higher in the albiglutide group compared with placebo (6.4 percent albiglutide 30 mg weekly versus 2 percent with placebo) [17]. In addition, up to 50 percent of patients developed low levels of anti-exenatide antibodies, with no relation to glycemic control or safety parameters.

Renal — Exenatide should **not** be used in patients with a creatinine clearance below 30 mL/min. In patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), monitoring of serum creatinine is warranted when initiating therapy and after the usual dose increase from 5 to 10 mcg [67].

There have been 78 reported cases of acute renal failure or renal insufficiency in patients using exenatide [67]. In a report of four patients, the time between initiation of exenatide and diagnosis of acute renal failure ranged from two to nine months [148]. All four patients presented with nausea, vomiting, and/or decreased fluid intake, and all were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics, which can contribute to the decline in renal function. None of the patients were taking nonsteroidal anti-inflammatory drugs (NSAIDs). After a dose reduction or withdrawal of exenatide, recovery of renal function was incomplete in three of the four patients. Renal biopsy in one patient showed ischemic glomeruli with moderate-to-severe interstitial fibrosis, tubular atrophy, and early diabetic nephropathy. The relationship between these findings and exenatide could not be determined.

There is limited experience in using liraglutide, albiglutide, and dulaglutide in patients with severe renal impairment (eGFR 15 to 29 mL/min) [149]. In liraglutide and albiglutide trials, the presence of mild-to-moderate renal impairment did not affect treatment outcomes [150-152]. However, there were too few patients with severe renal impairment to provide evidence for the safety and efficacy of these drugs in this population.

Other — In rodent studies, liraglutide and dulaglutide were associated with benign and malignant thyroid C-cell tumors [153,154]. In addition, stimulation of calcitonin release was reported in rats and mice exposed to exenatide and liraglutide [154,155]. This effect is mediated by the GLP-1 receptor [154].

It is unclear whether any effect is present in humans because humans have far fewer C-cells than rats, and expression of the GLP-1 receptor in human C-cells is very low [154]. There were no changes in calcitonin levels in short-term human studies, but medullary thyroid carcinoma may take years to develop, and its low prevalence complicates any quantification of risk [96,154]. The potential effect of long-acting GLP-1 receptor agonists and mimetics on thyroid C-cells in humans requires further investigation. Until such data are available, liraglutide, albiglutide, exenatide once weekly, and semaglutide are not recommended for use in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B [129,156].

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults".)

SUMMARY AND RECOMMENDATIONS

- Glucagon-like peptide-1 (GLP-1)-based therapies reproduce or enhance the actions of the naturally occurring peptide GLP-1. They affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake (table 1). They do not usually cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia. (See 'Glucagon-like peptide-1' above.)

- GLP-1 receptor agonists are not considered as initial therapy for the majority of patients with type 2 diabetes. (See 'Candidates' above and "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Choice of initial therapy'.)

- For patients who fail initial therapy, there are a number of agents that are available and can be used with metformin. The choice of therapy should be individualized based upon patient characteristics, preferences, and costs. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

  GLP-1 receptor agonists can be prescribed in combination with metformin (and/or another oral agent) for patients who fail initial therapy with one or two oral agents, particularly when weight loss or avoidance of hypoglycemia is a primary consideration, the glycated hemoglobin (A1C) level is close to target (within 1 to 1.5 percentage points), and cost is not a major barrier. A prior history of myocardial infarction or stroke might also favor choosing liraglutide as the second drug to be added to metformin. (See 'Candidates' above and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

  The exact role for GLP-1 receptor agonists among the myriad of other agents for management of type 2 diabetes is unclear. With long-term use of GLP-1 receptor agonists, weight loss can be substantial in a small fraction of treated patients and associated with other metabolic benefits. By comparison, insulin therapy generally requires only one injection and may be less expensive but is accompanied by hypoglycemia, albeit usually not severe, and weight gain. There are few long-term studies of GLP-1 receptor agonists to assess clinically important health outcomes (cardiovascular events, mortality), durability of glucose control or weight loss, or safety. Many questions remain unanswered regarding clinical use in type 2 diabetes, including long-term benefits and risks and their role in combination with other diabetes medications.

- When a decision has been made to use a GLP-1 receptor agonist, we prefer long- rather than short-acting GLP-1 receptor agonists. This is predominantly due to patient convenience. Among the long-acting agents, patient preference and payer coverage are important considerations in selecting an agent.

In the setting of a prior myocardial infarction or stroke, we suggest liraglutide or semaglutide (**Grade 2B**) based on the respective cardiovascular outcomes study results. It is unclear whether the progression of retinopathy seen in the semaglutide study is a direct effect of the drug or a consequence of rapid glycemic control similar to that seen in other settings. If semaglutide is prescribed to a patient with a history of diabetic retinopathy, consideration should be given to slower titration to avoid rapid declines in A1C and retinal screening within six months of drug initiation to detect progression of retinopathy. (See 'Choice of therapy' above.)

- Short-term studies using twice-daily exenatide, daily lixisenatide, daily liraglutide, or weekly albiglutide in combination with basal insulin (detemir and glargine) have demonstrated safety and efficacy. The addition of a GLP-1 agonist to basal insulin allows for achievement of glycemic targets at reduced insulin dose and amelioration of insulin-induced weight gain. However, the added benefit with regard to A1C lowering is very modest (usually <0.5 percent) and adds substantial expense as well as a second injection. (See 'Exenatide twice daily' above and 'Lixisenatide' above and 'Liraglutide' above and 'Albiglutide' above.)

- There are inadequate data to support the use of GLP-1 receptor agonists in combination with prandial insulin. Combination therapy with GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors does not provide additive glucose-lowering effects, and thus, the combination should be avoided. (See 'Candidates' above.)

- The side effects of GLP-1 receptor agonists are predominantly gastrointestinal, particularly nausea, vomiting, and diarrhea, and occur consistently in trials in 10 to 50 percent of patients. The risk of hypoglycemia is small. Hypoglycemic events may occur, however, when GLP-1 receptor agonists are given in conjunction with diabetes medications known to cause hypoglycemia (eg, insulin, sulfonylureas, glinides). (See 'Precautions and adverse effects' above.)

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Topic 1772 Version 51.0

GRAPHICS

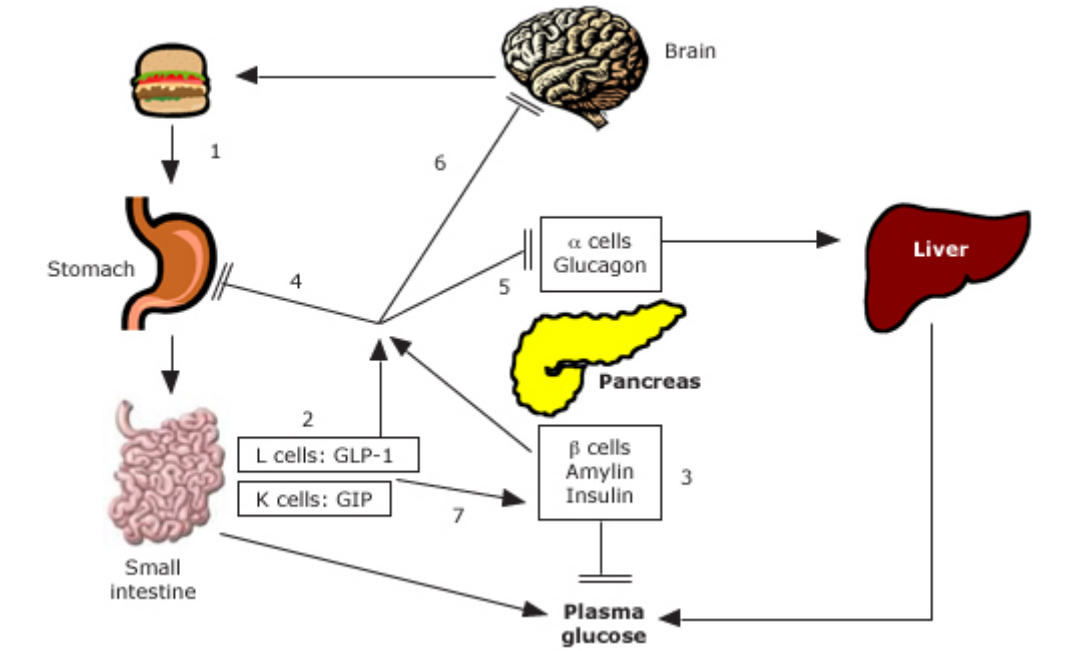
The role of GLP-1 in glucose homeostasis

	GLP-1
Deficiency	Type 2 diabetes, +/− type 1
Site of synthesis	Small intestinal L cells
Glucose-dependent stimulation of insulin secretion	Yes
Reduction of gastric emptying	Yes
Reduction of inappropriate glucagon secretion	Yes
Weight loss	Yes
Beta cell proliferation/regeneration	Yes - in animals

GLP-1: glucagon-like peptide-1.

Graphic 51832 Version 4.0

Multihormonal regulation of glucose

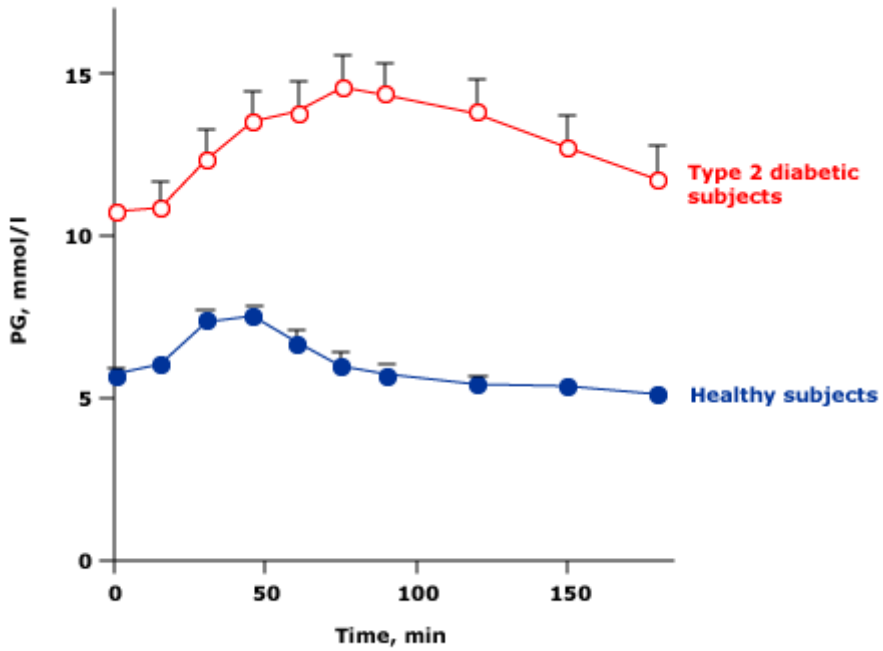


In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

GLP-1: glucagon-like peptide 1; GIP: glucose-dependent insulinotropic polypeptide, gastric inhibitory peptide.

Graphic 59551 Version 4.0

Plasma glucose concentrations during the 180 min period after meal ingestion



Data are means ±SE.

SE: standard error.

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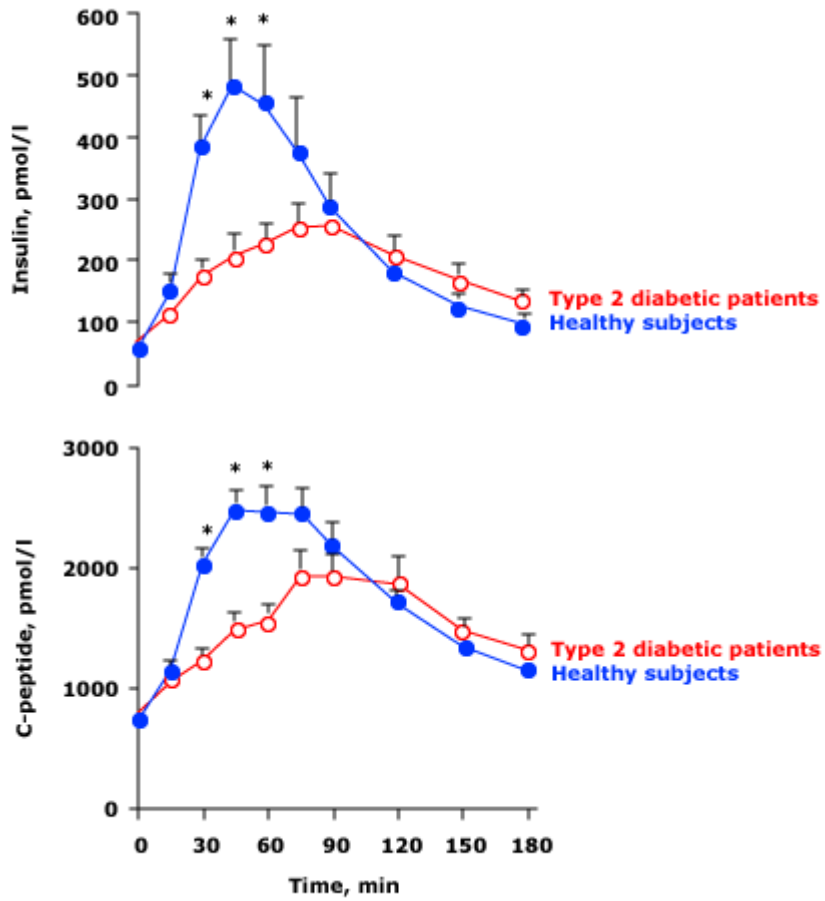
Graphic 59286 Version 2.0

Increase in plasma concentrations of insulin (top) and c-peptide (bottom) for type 2 diabetic patients and healthy subjects after ingestion of a mixed breakfast meal



Data are means ±SE.

SE: standard error.
* p <0.05 for differences between type 2 diabetic patients and healthy subjects.

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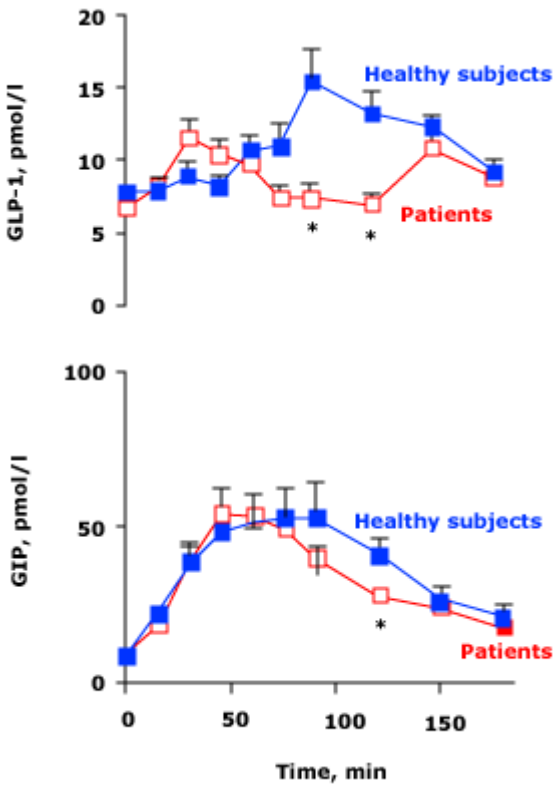
Graphic 72099 Version 2.0

GLP-1 concentrations (top) and GIP concentrations (bottom) using NH2-terminal assays



Data are means ±SE.

GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic polypeptide; SE: standard error.
* p <0.05 for differences between type 2 diabetic patients and healthy subjects.

Modified with permission from: Vilsboll T, Krarup T, Deacon C, et al. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. Diabetes 2001; 50:609. Copyright © 2001 The American Diabetes Association.

Graphic 81642 Version 2.0

Contributor Disclosures

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Conflict of interest policy