Amylin analogs for the treatment of diabetes mellitus

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INTRODUCTION — Despite advances in options for the treatment of diabetes, optimal glycemic control is often not achieved [1]. Hypoglycemia and weight gain associated with therapy may interfere with the implementation and long-term application of "intensive" therapies [2-4]. Treatment of type 1 diabetes is directed at physiologic insulin replacement. Many patients with type 2 diabetes also ultimately require insulin therapy as a result of progressive beta cell dysfunction [5]. Starter insulin regimens (such as basal insulin monotherapy) for patients with type 2 diabetes commonly require repeated intensification over time to achieve even modest glycated hemoglobin (A1C) reductions [6]. Therefore, other therapeutic approaches are needed.

Glucose homeostasis is dependent on a complex interplay of multiple hormones that may be targets for a multifaceted treatment approach: insulin and amylin, produced by pancreatic beta cells; glucagon, produced by pancreatic alpha cells; and gastrointestinal peptides, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP; gastric inhibitory polypeptide) (figure 1) [7]. Abnormal regulation of these substances may contribute to the clinical presentation of diabetes.

The mechanism of action and therapeutic utility of amylin analogs will be reviewed here. GLP-1-based therapies and overviews of pharmacologic therapy for type 1 and type 2 diabetes are presented separately. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus" and "Management of blood glucose in adults with type 1 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".)

AMYLIN — Amylin is a 37-amino acid peptide that is stored in pancreatic beta cells and is co-secreted with insulin [8]. Amylin and insulin levels rise and fall in a synchronous manner (figure 2) [7]. Amylin and insulin have complementary actions in regulating nutrient levels in the circulation. Amylin is deficient in type 1 diabetes and relatively deficient in insulin-requiring type 2 diabetes (figure 2) [7].

Amylin affects glucose control through several mechanisms, including slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake (table 1). Glucagon-like peptide 1 (GLP-1) exhibits similar properties as amylin, with the exception of insulin secretory effects. Amylin, unlike GLP-1, does not have insulin secretory effects, but both regulate hyperglycemia in part through amelioration of inappropriate glucagon secretion and gastric emptying. GLP-1 and amylin appear to have differing magnitudes of physiologic effects and bind to different receptors in the area postrema, the part of the brain that may be key for their effects on satiety [9,10]. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus".)

PRAMLINTIDE — Pramlintide is a stable, soluble, nonaggregating, equipotent amylin analog that is administered by mealtime subcutaneous injection. It is available for use for both type 1 and insulin-treated type 2 diabetes. Pramlintide reproduces the actions of amylin and controls glucose without causing weight

gain. Many questions remain unanswered regarding clinical use and long-term outcomes with this class of drug, and therefore, the exact role for amylin analogs among the myriad of other agents for diabetes management is unclear.

Mechanism of action — Pramlintide regulates postmeal blood glucose levels by slowing gastric emptying, promoting satiety, and suppressing the abnormal postprandial rise of glucagon in patients with diabetes [11-13]. Thus, endogenous (liver-derived) and exogenous (meal-derived) glucose influx are better regulated, allowing exogenous insulin therapy to more easily match physiologic needs. These effects are glucose dependent and are overridden as serum glucose levels fall [14]. Pramlintide does not cause hypoglycemia in the absence of therapies that otherwise cause hypoglycemia. Supraphysiologic doses of pramlintide do not provoke hypoglycemia in normal subjects [15], and pramlintide does not interfere with recovery from insulin-induced hypoglycemia [16,17].

Efficacy — Pramlintide has been studied in randomized controlled trials in both type 1 and type 2 diabetes [18-23].

- **Type 1 diabetes** – In type 1 diabetes, 30 to 60 mcg of pramlintide administered subcutaneously with meals resulted in sustained, albeit modest (<1 percentage point) reductions in glycated hemoglobin (A1C) over the 52-week trial (figure 3A-B) [18]. More than twice as many patients (25 versus 11.3 percent) achieved an A1C of less than 7 percent in the treatment group than in the placebo group, with no increase in insulin dose or incidence of severe hypoglycemia. Modest reductions in body weight (mean of 0.5 kg) were seen in the treatment group, compared with weight gain in patients receiving insulin only.

  Similar results were found in a second large, randomized trial evaluating pramlintide at 60 mcg three to four times per day [19]. In this study, weight loss was more prevalent in obese patients compared with patients with normal body weight and was independent of reports of nausea.

  Pramlintide is also under investigation for use with closed-loop insulin delivery systems, which are under development for management of type 1 diabetes [24,25]. Meal challenges are one of the greatest hurdles for maintaining glucose control with the use of closed-loop control systems. Preliminary, nonrandomized data suggest that pramlintide is associated with delayed time to peak plasma glucose excursion and reduced peak postprandial rise in glucose and area under the curve when used in combination with closed-loop systems [24,25]. (See "Management of blood glucose in adults with type 1 diabetes mellitus".)

- **Type 2 diabetes** – In patients with type 2 diabetes, pramlintide has been shown to reduce A1C and weight (figure 3A-B) [20-22,26]. When added to existing insulin therapy with or without a sulfonylurea or metformin, reductions in A1C (mean 0.62 percentage points) and weight (1.4 kg) were seen with 120 mcg but not 90 mcg of pramlintide given twice daily [20]. Pooled, post hoc analyses showed that reductions in insulin requirements and body weight were greatest in more obese patients [27].

  In a 24-week trial of patients with inadequately controlled type 2 diabetes, the addition of premeal pramlintide to basal insulin with or without oral agents had similar glycemic efficacy as the addition of premeal rapid acting insulin analogs (A1C reduction of approximately 1 percentage point) [23]. Patients randomly assigned to pramlintide maintained their weight, whereas those assigned to rapid-acting insulin gained weight (mean 4.7 kg). Pramlintide was associated with fewer hypoglycemic events compared with prandial insulin.

  In addition to modest reductions in A1C and body weight, pramlintide has been associated with reductions in postprandial glucose excursions [28] and in surrogate markers of cardiovascular risk and oxidative stress [29,30]. The clinical implications of these findings are unknown.

Side effects and adverse events — Mild to moderate nausea is the most commonly reported side effect and generally dissipates by four weeks. Nausea can be minimized by slow upward dose titration and is less

common in patients with type 2 diabetes [20-22].

Severe hypoglycemia in type 1 diabetes was increased fourfold during the first four weeks in one study when patients were started at full doses of pramlintide at randomization without reduction in insulin dose [19]. In a subsequent study, insulin dose was reduced by 25 percent at initiation of pramlintide therapy, which was titrated to the maximum dose over a period of one to two months. With this strategy, there was no increase in hypoglycemia. Premeal insulin doses stabilized at an average of 17 percent lower in pramlintide-treated patients compared with placebo by study end [31]. Hypoglycemia was less frequent in studies of patients with type 2 diabetes [20-22].

Small studies suggest that the increased incidence of hypoglycemia observed in patients with type 1 diabetes is related to mismatched timing of prandial insulin relative to peak glucose levels [32]. Pramlintide delays gastric emptying, resulting in blunted but delayed postmeal peak glucose. Thus, rapid-acting insulin analogs taken pre-meal may peak before the glucose peak occurs, increasing the risk of early hypoglycemia followed by delayed hyperglycemia. This is analogous to the pattern observed in patients with gastroparesis [33]. It is unknown whether regular human insulin or post-meal rapid acting insulin analogs ameliorate this problem.

Dose and administration — Pramlintide is only approved for use in patients with type 1 and type 2 diabetes taking prandial insulin. Pramlintide precipitates above a pH of 5.5 and must be injected separately from insulin at a different site [34]. The optimal timing for administration is immediately before a meal [35,36]. According to the approved labeling, premeal insulin doses (including premixed insulin) should be reduced by 50 percent and should subsequently be titrated upward to achieve euglycemia once the target pramlintide dose is reached [37]. However, as noted above, most patients require a smaller reduction in prandial insulin. Patients with near-optimal glycemic control on insulin pumps who utilize the extended wave bolus feature (square wave or dual wave) require minimal prandial insulin dose adjustments (<10 percent) after initiation of pramlintide [32,38].

Pramlintide should not be administered to patients with severe hypoglycemia unawareness. Pramlintide should only be administered before meals that contain at least 250 calories or 30 grams of carbohydrates. Patients may need to administer their prandial insulin after meals until they become familiar with the degree of satiety and resulting reduction of carbohydrate intake that may occur. Another strategy is to substitute human regular insulin for the rapid-acting analogue. This strategy may better match insulin with food.

The recommended starting dose for type 1 diabetes is 15 mcg before each meal, with increases of 15 mcg increments every three to seven days, as tolerated, to a goal of 60 mcg before each meal. Persistent nausea should prompt backward titration until resolved.

The recommended initial dose for type 2 diabetes is 60 mcg, titrated upward as tolerated to 120 mcg with each meal.

Pramlintide slows gastric emptying and may delay the rate of absorption of oral medications. Patients with gastroparesis should not use pramlintide. Oral medications that require rapid absorption for effectiveness should be administered either one hour before or two hours after injection of pramlintide.

SUMMARY AND RECOMMENDATIONS — Pramlintide reproduces the actions of the naturally occurring peptide hormone, amylin, and controls glucose without causing weight gain. Many questions remain unanswered regarding clinical use and long-term outcomes with this class of drug, and therefore, the exact role for amylin analogs among the myriad of other agents for diabetes management is unclear [39].

We suggest an individualized approach to initiating these therapies.

- Pramlintide is only approved for use in patients also taking prandial insulin. However, it requires injections with each meal in the setting of type 1 diabetes and at least twice daily in type 2 diabetes. It cannot be mixed in a syringe with insulin. Pramlintide therapy requires careful patient education and

monitoring to avoid severe hypoglycemia and should be instituted in collaboration with a diabetes educator experienced in its use. (See 'Pramlintide' above.)

- Pramlintide could be considered in motivated patients with type 1 diabetes suboptimally controlled with insulin therapy alone, particularly in patients taking multiple daily injections or insulin pump therapy who gain weight despite lifestyle intervention.
- Pramlintide may be considered for motivated patients with type 2 diabetes inadequately controlled on prandial insulin who are overweight or experience weight gain refractory to lifestyle measures.
- There are inadequate data to support the following uses of pramlintide:
  - Pramlintide in patients not requiring insulin
  - Pramlintide in patients with a history of severe hypoglycemia or hypoglycemia unawareness
  - Combination therapy of pramlintide with exenatide or other glucagon-like peptide-1 (GLP-1)-based therapies

GLP-1-based therapies are reviewed separately. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus".)

REFERENCES

1. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004; 291:335.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.
3. Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes 1997; 46:271.
4. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. Diabetes Care 2001; 24:1711.
5. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes 1995; 44:1249.
6. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009; 361:1736.
7. Buse JB, Weyer C, Maggs DG. Amylin replacement with Pramlintide in type 1 and type 2 diabetes: a physiological approach to overcome barriers with insulin therapy. Clinical Diabetes 2002; 20:137.
8. Johnson KH, O'Brien TD, Hayden DW, et al. Immunolocalization of islet amyloid polypeptide (IAPP) in pancreatic beta cells by means of peroxidase-antiperoxidase (PAP) and protein A-gold techniques. Am J Pathol 1988; 130:1.
9. Züger D, Forster K, Lutz TA, Riediger T. Amylin and GLP-1 target different populations of area postrema neurons that are both modulated by nutrient stimuli. Physiol Behav 2013; 112-113:61.
10. Asmar M, Bache M, Knop FK, et al. Do the actions of glucagon-like peptide-1 on gastric emptying, appetite, and food intake involve release of amylin in humans? J Clin Endocrinol Metab 2010; 95:2367.
11. Kong MF, Stubbs TA, King P, et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. Diabetologia 1998; 41:577.

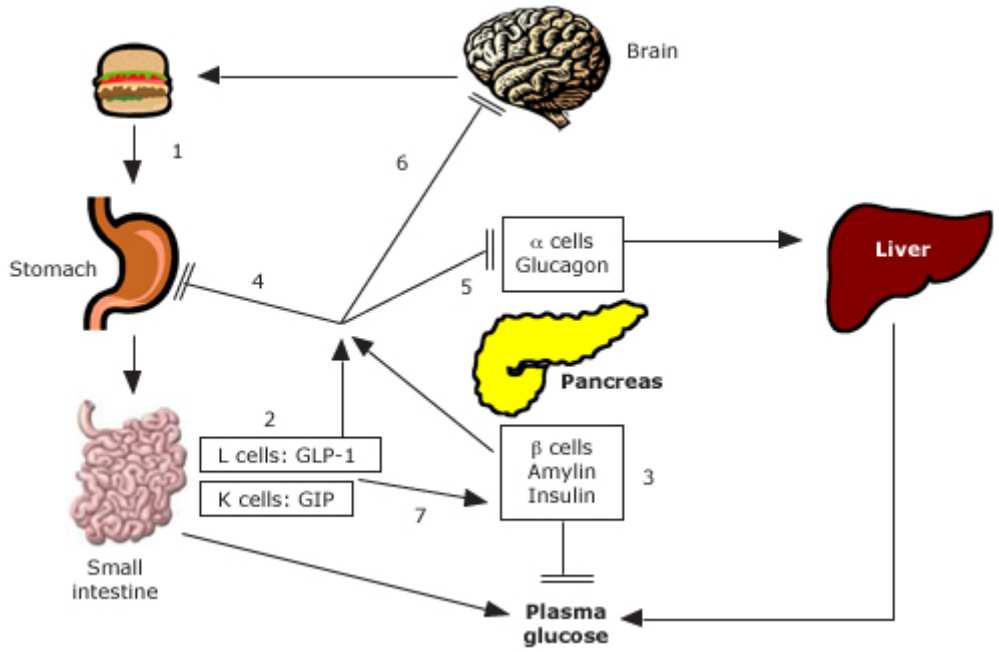
12. Fineman MS, Koda JE, Shen LZ, et al. The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. Metabolism 2002; 51:636.
13. Woerle HJ, Albrecht M, Linke R, et al. Impaired hyperglycemia-induced delay in gastric emptying in patients with type 1 diabetes deficient for islet amyloid polypeptide. Diabetes Care 2008; 31:2325.
14. Kolterman OG, Schwartz S, Corder C, et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. Diabetologia 1996; 39:492.
15. Bretherton-Watt D, Gilbey SG, Ghatei MA, et al. Very high concentrations of islet amyloid polypeptide are necessary to alter the insulin response to intravenous glucose in man. J Clin Endocrinol Metab 1992; 74:1032.
16. Heise T, Heinemann L, Heller S, et al. Effect of pramlintide on symptom, catecholamine, and glucagon responses to hypoglycemia in healthy subjects. Metabolism 2004; 53:1227.
17. Amiel SA, Heller SR, Macdonald IA, et al. The effect of pramlintide on hormonal, metabolic or symptomatic responses to insulin-induced hypoglycaemia in patients with type 1 diabetes. Diabetes Obes Metab 2005; 7:504.
18. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care 2002; 25:724.
19. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004; 21:1204.
20. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2003; 26:784.
21. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. Diabetes Technol Ther 2002; 4:51.
22. Riddle M, Frias J, Zhang B, et al. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. Diabetes Care 2007; 30:2794.
23. Riddle M, Pencek R, Charenkavanich S, et al. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. Diabetes Care 2009; 32:1577.
24. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012; 35:1994.
25. Sherr JL, Patel NS, Michaud CI, et al. Mitigating Meal-Related Glycemic Excursions in an Insulin-Sparing Manner During Closed-Loop Insulin Delivery: The Beneficial Effects of Adjunctive Pramlintide and Liraglutide. Diabetes Care 2016; 39:1127.
26. Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2011; 13:169.
27. Hollander P, Maggs DG, Ruggles JA, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. Obes Res 2004; 12:661.
28. Kovatchev BP, Crean J, McCall A. Pramlintide reduces the risks associated with glucose variability in type 1 diabetes. Diabetes Technol Ther 2008; 10:391.
29. Ceriello A, Lush CW, Darsow T, et al. Pramlintide reduced markers of oxidative stress in the postprandial period in patients with type 2 diabetes. Diabetes Metab Res Rev 2008; 24:103.

30. Wysham C, Lush C, Zhang B, et al. Effect of pramlintide as an adjunct to basal insulin on markers of cardiovascular risk in patients with type 2 diabetes. Curr Med Res Opin 2008; 24:79.
31. Levetan C, Want LL, Weyer C, et al. Impact of pramlintide on glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps. Diabetes Care 2003; 26:1.
32. King AB. Minimal reduction in insulin dosage with pramlintide therapy when pretreatment near-normal glycemia is established and square-wave meal bolus is used. Endocr Pract 2009; 15:229.
33. Ishii M, Nakamura T, Kasai F, et al. Altered postprandial insulin requirement in IDDM patients with gastroparesis. Diabetes Care 1994; 17:901.
34. Schmitz O, Brock B, Rungby J. Amylin agonists: a novel approach in the treatment of diabetes. Diabetes 2004; 53 Suppl 3:S233.
35. Creutzfeldt W. The [pre-] history of the incretin concept. Regul Pept 2005; 128:87.
36. Maggs DG, Fineman M, Kornstein J, et al. Pramlintide reduces postprandial glucose excursions when added to insulin lispro in subjects with type 2 diabetes: a dose-timing study. Diabetes Metab Res Rev 2004; 20:55.
37. Weyer C, Gottlieb A, Kim DD, et al. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. Diabetes Care 2003; 26:3074.
38. King AB. Comparison of the post-meal glucose response to different insulin bolus waveforms in insulin pump- and pre-meal pramlintide-treated type 1 diabetes patients. Diabetes Technol Ther 2010; 12:105.
39. Riddle MC, Drucker DJ. Emerging therapies mimicking the effects of amylin and glucagon-like peptide 1. Diabetes Care 2006; 29:435.

Topic 1758 Version 10.0

GRAPHICS

Multihormonal regulation of glucose

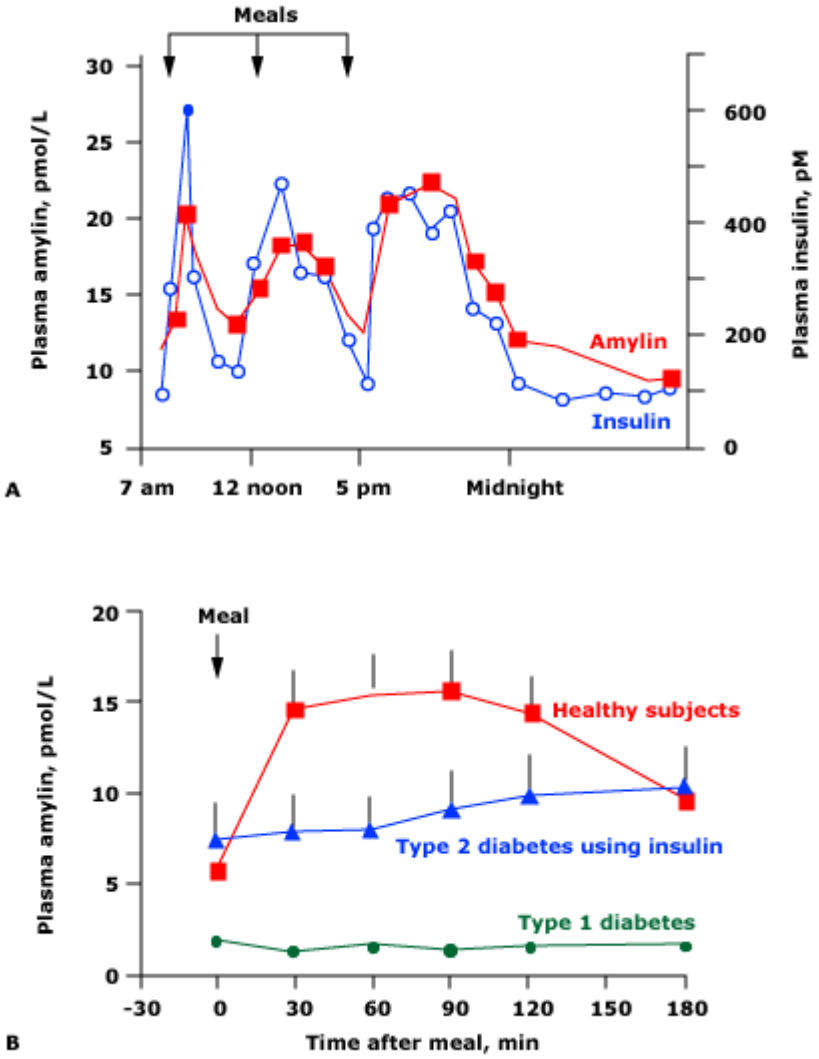


In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (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

Twenty-four-hour plasma amylin



(A) Twenty-four-hour plasma insulin and amylin profiles in healthy subjects. (B) Mean amylin ±standard deviation versus time after a meal. Amylin response is absent in patients with type 1 diabetes and impaired in insulin-requiring patients with type 2 diabetes.

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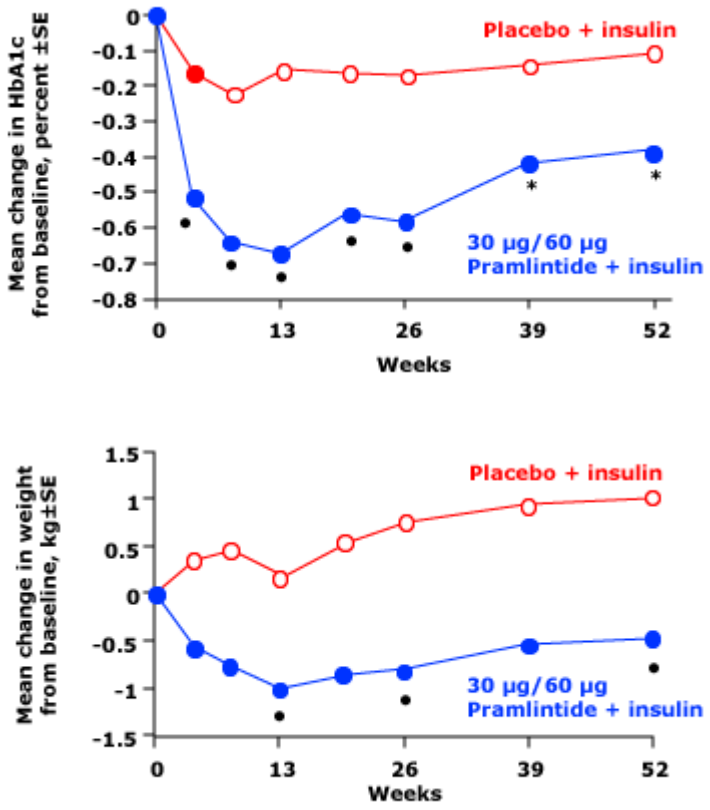
Graphic 74823 Version 3.0

The role of amylin in glucose homeostasis

	Amylin
Deficiency	Type 1, type 2 diabetes
Site of synthesis	Pancreatic beta cells
Glucose-dependent stimulation of insulin secretion	No
Reduction of gastric emptying	Yes
Reduction of inappropriate glucagon secretion	Yes
Weight loss	Yes
Beta cell proliferation/regeneration	Unknown
Therapies	Pramlintide (Symlin)
Target population	Type 1 diabetes and insulin-treated type 2 diabetes

Graphic 79703 Version 1.0

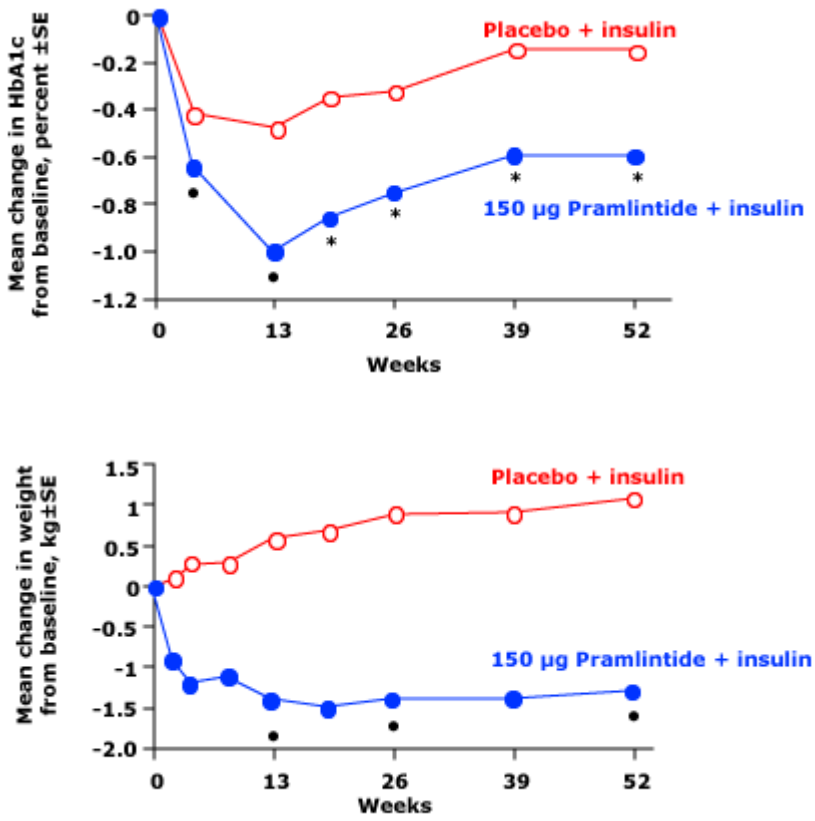
Mean change ± standard deviation in A1c and body weight in patients with type 1 diabetes treated with insulin plus either pramlintide or placebo



HbA1C: glycated hemoglobin.
* p<0.05.
• p<0.001.

Graphic 79842 Version 2.0

Mean change ± standard deviation in A1c and body weight in patients with type 2 diabetes treated with insulin plus either pramlintide or placebo



HbA1c: glycated hemoglobin.
* p<0.05.
• p<0.001.

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Graphic 60521 Version 3.0

Contributor Disclosures

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