– REVIEW ARTICLE —

New Potential Adjuncts to Treatment of Children With Type 1 Diabetes Mellitus

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ABSTRACT: Insulin administration is the primary therapy for type 1 diabetes mellitus (T1DM). Current available insulin therapies do not successfully enable children with T1DM to reach glycemic goals without side effects such as hypoglycemia and weight gain. Pramlintide is a synthetic analog of human amylin that acts in conjunction with insulin to delay gastric emptying and inhibit the release of glucagon and is indicated for use in patients with type 1 and type 2 diabetes. Recent studies in adult patients have examined the role of glucagon-like peptide 1 (GLP-1) and agents that bind to its receptor in type 1 diabetes. It is hypothesized that a major component of the glycemic effect is attributable to the known action of GLP-1 to delay gastric emptying and to inhibit glucagon secretion. Further studies with the use of amylin analogs and long-acting GLP-1 agonists as congeners with insulin in T1DM are indicated in children. In recent years, our better understanding of the pathophysiology of diabetes has led to the development of new therapies for diabetes. This article reviews the potential use of these newer pharmacologic agents as adjunctive therapy in T1DM in children and adolescents. (Pediatr Res 65: 370-374, 2009)

Type 1 diabetes mellitus (T1DM) is an autoimmune process with a strong genetic component causing destruction and dysfunction of the pancreatic β -cells. It involves both insulin and amylin deficiencies. Insulin administration is the primary therapy for T1DM.

Current standards of care recommend intensive diabetes management and lowering hemoglobin A1c (HbA1c) to as close to normal as possible. However, 87 years after the discovery of insulin, physicians and patients still struggle for optimal diabetes control because of limitations of insulin therapy.

The Diabetes Control and Complication Trial demonstrated the direct relationship between glycemic control as predicted by HbA1c and onset and prevention of microvascular complications (1,2). Studies show a strong correlation between HbA1c and plasma glucose levels both at fasting and over postprandial periods (3,4). Studies also suggest that postprandial hyperglycemia is an important risk factor for the development of macrovascular disease (5,6). Increased glycemic variability seems to correspond with elevated markers of oxidative stress and inflammation associated with cardiovascular disease (7). Thus, reductions in postprandial glycemic variability may be an important step in lowering complications related to diabetes (8). However, as insulin doses are pushed in an attempt to normalize blood glucose after meals, risk of hypoglycemia and excessive weight gain occur.

This failure to achieve and maintain euglycemia in majority of children with T1DM provides an impetus to seek newer adjunctive therapies that are both safe and effective. In recent years, our better understanding of the pathophysiology of diabetes has led to the development of new therapies for diabetes. This article reviews the potential use of newer pharmacologic agents as adjunctive therapy in T1DM in children.

Pathophysiology of type 1 diabetes and rationale for adjunctive therapy. The postprandial glucose profile is determined by several factors: the rate and extent of glucose absorption, secretory patterns of various hormones (insulin, glucagon, amylin, and incretin hormones), and their effects on hepatic and peripheral tissue glucose metabolism. Studies have shown that the postmeal responses of insulin, glucagon, and glucose differ between individuals with and without diabetes. Typically in a person without diabetes, the blood glucoses are tightly controlled (9). Postprandially, the concurrent increases in blood glucose and insulin results in suppression of hepatic glucose production by suppressing glycogenolysis and gluconeogenesis and increase in glucose uptake and utilization by the peripheral tissues particularly muscle and fat. In those with diabetes, insulin release is deficient, paradoxical rise in glucagon contributes to postprandial hyperglycemia (10).

Role of gastric emptying. Gastric-emptying rate is an important determinant of postprandial blood glucose. The rate of gastric emptying has a direct effect on the rate of glucose appearance after a meal as a result of absorption of glucose and simple carbohydrates from the proximal small intestine (11). Postprandial glucose can be as much as 34% higher in normal healthy subjects who empty their stomachs rapidly than in those who have a slower gastric emptying rate (12). Gastric emptying in patients with diabetes is an area of much controversy. There are studies that suggest that there is accelerated, normal, and delayed gastric emptying in T1DM (13–

Abbreviations: GLP-1, Glucagon-like peptide-1; GLP-1R, Glucagon-like peptide-1 Receptor; HbA1c, Hemoglobin A1c; pdx1, Pancreatic duodenal homeobox 1; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

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Table 1. Mechanism for adjunctive therapy in T1DM

Class of drug	Drug	Main mechanism of action
Synthetic amylin analogs	Pramlintide	Delayed gastric emptying, glucagon suppression
GLP-1 receptor agonists	Exenatide	Delayed gastric emptying, glucagon suppression, (±enhancement of insulin secretion)

15). In T1DM patients and healthy subjects, acute hyperglycemia slows gastric emptying of both solids and nutrient liquids, when compared with euglycemia (16,17). Patients with known autonomic neuropathy and longstanding diabetes have gastroparesis (18).

Rationale for adjunctive therapy. Glucose homeostasis is dependent on the complex interplay of multiple hormones: insulin, glucagon, amylin, and gastrointestinal peptides, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide. By the addition of adjunctive therapies, glucose homeostasis may be achieved by a more balanced approach (19). The mechanism of action for adjunctive therapies in T1DM is summarized in Table 1.

REPLACEMENT OF AMYLIN AS PHYSIOLOGIC APPROACH TO THE TREATMENT OF DIABETES

Amylin physiology and pathophysiology. In 1987, it was reported that pancreatic beta cells secrete another hormone, which was identified as amylin (20). In type 1 diabetes, owing to the destruction of the β -cells, patients have an absolute deficiency of both insulin and amylin. Amylin and insulin have complementary actions in regulating glucose homeostasis. Amylin has glucose lowering effects by (1) suppression of endogenous glucagon production, especially in the postprandial state; (2) slowing of gastric emptying time; and (3) reduction of postprandial hepatic glucose production. It also causes centrally mediated induction of satiety.

Effects on gastric emptying. Amylin seems to normalize gastric motility and gastric-emptying time (19,21). Amylin thus regulates delivery of nutrients to the small intestine and the rate of glucose appearance in the blood.

Pramlintide: synthetic analog of amylin. Pramlintide is a synthetic analog of human amylin. In 2005, pramlintide was approved by the Food and Drug administration for use in patients with diabetes treated with mealtime insulin who have not achieved glycemic goals. Pramlintide reduces postprandial glycemia and glucose fluctuations, resulting in improved glycemic control without associated weight gain (22).

Native amylin is glue like and unstable as a compound solution and has a propensity to aggregate and adhere to the surfaces. Pramlintide has similar physiologic effects as native amylin. Pramlintide is a peptide and is therefore administered systemically, *e.g.* via s.c. injection. It does not impede the glucagon response to hypoglycemia or attenuate the effects of counterregulatory hormones triggered by hypoglycemia (catecholamines, growth hormone, cortisol, and glucagon) (23).

Clinical studies in type 1 diabetes. Short-term clinical studies in patients with T1DM showed that mealtime amylin

replacement with pramlintide slows the rate of nutrient delivery from the stomach to the small intestine (24,25) and prevents an abnormal increase in glucagon after meals (26,27). All of these effects were achieved with pramlintide doses of 30 or 60 μ g, which resulted in plasma pramlintide concentrations similar to the postprandial amylin levels seen in healthy subjects. In our experience in adolescents with T1DM, increasing the insulin dose by 60% before a meal did not correct immediate postprandial hyperglycemia. Pramlintide was effective in decreasing immediate postprandial hyperglycemia in adolescents with T1DM (28,29). We have also found that postprandial hyperglycemia is considerably reduced in adolescents with T1DM when treated with premeal 30 μ g pramlintide and postmeal insulin, without significant side effects (unpublished data).

Long-term clinical studies in adults with T1DM show that adjunctive therapy with pramlintide facilitates further improvement of overall glycemic control without the increase in body weight and/or severe hypoglycemia (30–32). In a multicenter study of 480 T1DM patients (16–70 y of age), Whitehouse *et al.* (30) showed that treatment with pramlintide led to a mean reduction in HbA1c of 0.67% from baseline to week 13 that was significantly greater than the reduction with placebo (0.16%); a significant treatment difference was sustained through week 52. Ratner *et al.* (31) showed that the addition of pramlintide 60 μ g three times or four times daily to insulin led to significant reductions in HbA1c of 0.29% and 0.34%, respectively, compared with a 0.04% reduction in placebo group, over 52 wk.

Effects on weight. Several studies have assessed the effect of pramlintide on weight control in adults with T1DM. Ratner *et al.* (31) reported a significant reduction in body weight from baseline to week 52 of 0.4 kg in the pramlintide treatment groups, compared with a 0.8-kg gain in body weight in the placebo group. A 29-wk study by Edelman *et al.* (32) of 296 patients with T1DM showed that pramlintide treatment significantly reduced weight (pramlintide -1.3 ± 0.30 , placebo $+1.2 \pm 0.30$ kg), despite equivalent HbA1c reductions relative to placebo.

The mechanism underlying the observed weight reduction with pramlintide is not fully understood. The effects seem to be centrally mediated. High-density amylin sites are identified in the dorsal raphe and nucleus acumbens, the regions in brain that control feeding behavior. Pramlintide's effect on appetite targets peripheral episodic satiety signals (33). In rodents, amylin dose dependently reduced food intake and body weight by affecting the size and duration of meals (34,35). In a randomized, double blind, placebo-controlled crossover study, preprandial injection of pramlintide elicited a 20% reduction in *ad libitum* food intake in insulin-treated patients with T2DM (36). In another study, low-dose pramlintide reduced food intake and meal duration in healthy, normal-weight subjects (37).

Other effects. Pramlintide reduced postprandial markers of oxidative stress, including nitrotyrosine and oxidized LDL that are associated with increased risk of cardiovascular disease and diabetic microvascular complications in a study (38).

Adverse effects and practical considerations. The most common adverse effects include nausea, vomiting, and an-

orexia. Rates of nausea in studies have ranged from 9.5 to 59% with most cases being mild to moderate in nature and resolving in 2-8 weeks. Pramlintide in itself does not cause hypoglycemia. When coadministered with insulin, it increases the risk of insulin-induced hypoglycemia. Insulin doses may need to be reduced by 20-50%. Pramlintide should be avoided in patients with gastroparesis because it slows gastric emptying. Currently, weight-based pramlintide dosing information is unavailable. In adults with T1DM, pramlintide is usually initiated at a dose of 15 μ g and titrated in 15- μ g increments to a final dose of 60 μ g based on tolerability to nausea. If the 45- μ g and 60- μ g doses are not well tolerated, a maintenance dose of 15–30 μ g can be used. Pramlintide is taken by s.c. injection just before mealtimes and should be administered in a separate syringe at an injection site distinct from that of concurrent insulin. Pramlintide is yet to be approved for use in children. In general, candidates for treatment include patients who have failed to achieve glycemic control despite individualized insulin management, and who are able to monitor blood glucose frequently and are under the care of healthcare professional skilled in the use of insulin.

In conclusion, amylin replacement with pramlintide as an adjunct to insulin therapy potentially represents a novel and more physiologic approach toward improved metabolic control in children with T1DM. However, more short-term and long-term studies with pramlintide are needed in the pediatric population.

DIABETES AND THE INCRETIN EFFECT

The incretin effect was first described after the observation that insulin responses to oral glucose exceeded those measured after administration of equivalent amount of i.v. glucose. In healthy individuals, incretin effect is responsible for 50–70% of insulin response to oral glucose (39). Most postprandial hormones have incretin-like effects; the two predominant incretin hormones are gastric inhibitory peptide and GLP-1. GLP-1 seems to be responsible for most of incretin effect on pancreatic beta-cell function.

Physiology of GLP-1. GLP-1 is released from intestinal L-cell, which is the major source, with small quantities released from pancreatic alpha cells. It exerts its actions through a specific G protein-coupled receptor expressed on islet β -cells (40). GLP-1 receptors (GLP-1R) are found in many tissues, including pancreatic islets, stomach, small intestine, kidney, lung, brain, and pituitary gland. It is a potent suppressor of glucagon in vivo. The insulinotropic action of GLP-1 is glucose dependent. It also stimulates insulin synthesis through enhancing proinsulin gene transcription (41). The biologic half-life of GLP-1 is very short, about 2 min, because of enzymatic degradation by dipeptidyl peptidase-IV and renal clearance (42). It inhibits both gastric acid secretion and gastric emptying after meals via vagal afferent central mechanisms (43,44) and contributes to reducing postprandial glycemic excursions (44).

GLP-1 in diabetes. Studies have suggested that endogenous secretion of GLP-1 is defective in T2DM (45). The existing literature about GLP-1 in T1DM produces conflicting results.

A study has reported a lack of GLP-1 secretion in patients with T1DM in response to a meal (46). Another study has reported normal GLP-1 response to meal among patients with T1DM compared with healthy subjects (47). However, fasting GLP-1 levels were lowest in patients with T1DM. In one pediatric study, decreasing β -cell function during the first year of T1DM was associated with increasing postprandial blood glucose, glucagon, and GLP-1 (48).

Effect on glycemic excursions after meals in T1DM. Several small, short-term studies in adults suggest that GLP-1 may have the potential for therapeutic use in T1DM (49). Continuous i.v. infusion of GLP-1 without insulin in patients with T1DM who had detectable insulin responses to meals, prevented a rise in blood glucose levels after ingestion of a meal after overnight fasting (50). This was accompanied by suppression of the abnormal glucagon response to the meal. There is potential for s.c. GLP-1 to improve short-term glycemic control in patients with T1DM when administered before meals in addition to insulin. In a study of patients with T1DM and absent residual insulin secretion, postprandial blood glucose levels were significantly reduced with GLP-1 in a 5-d study period without an increase in significant hypoglycemia or a change in dose of insulin (51). In another study in patients with T1DM, where three patients had residual insulin secreting capacity, GLP-1 when compared with placebo reduced glucagon levels by 50% and increased C-peptide levels to a small but significant degree (52).

GLP-1 and pancreas. In addition to these glucoregulatory effects, GLP-1 may be important in beta-cell proliferation and survival, making it an attractive candidate for assessment in prolongation of beta cell survival (53). In animal studies, GLP-1 is associated with induction of pancreatic duodenal homeobox 1 (pdx1) gene expression (54,55). Pdx1 is a transcription factor, which is primarily expressed in the endocrine pancreas and subsets of enteroendocrine cells in the duodenum and is critical for pancreatic development and formation (55). GLP-1 actions may be mediated through pdx1, and thus influence beta-cell proliferation and survival (56). Furthermore, GLP-1 regulates a subset of genes, including proinsulin, GLUT-2, and glucokinase that are known transcriptional targets of pdx1 action (57). Apoptosis-related cell death is a feature of both type 1 and type 2 diabetes mellitus. GLP-1 has antiapoptotic properties independent of its action on glucose regulation and islet proliferation. In mice with streptozotocininduced diabetes, which causes apoptosis, treatment with exendin-4, a GLP-1 receptor analog, resulted in euglycemia significantly longer than those that were not treated with GLP-1 (58). The increase in β -cell mass observed after treatment with GLP-1R agonists is thought to arise from direct stimulation of β -cell proliferation, and via enhancement of islet neogenesis (59). More recent evidence suggests that GLP-1 also preserves β -cell mass via inhibition of apoptosis (60). These parameters are difficult to assess in human subjects. There is evidence that experimentally induced changes in β -cell mass of nonobese diabetic mice early in the course of the autoimmune process can inhibit the subsequent development of disease (61). As T1DM is thought to result from progressive β -cell destruction and failure to regenerate β -cell mass, it remains possible that intervention with GLP-1R agonists will modify the natural course of β -cell destruction and/or regeneration, resulting in clinically detectable improvements in insulin secretion and glucose control.

Exenatide. Exenatide is a synthetic version of exendin-4, a naturally occurring 39-amino acid peptide originally isolated from the salivary secretions of the lizard *Heloderma suspectum*. It is a partial structural analog of human GLP-1, sharing 53% amino acid sequence homology. It binds to and activates human GLP-1 receptor. It is not a substrate for dipeptidyl peptidase-IV and has a much longer half-life than GLP-1.

Clinical studies of exenatide in T1DM. Exendin-4 administration before a meal in adults with T1DM resulted in a significant reduction in postprandial blood glucose values which were comparable with those of healthy control subjects. Plasma glucagon concentrations were abnormally high compared with those of control subjects with insulin alone, but the concentrations were reduced and did not differ from control subjects after exendin-4 was added. Antihyperglycemic effects of the drug were attributed to suppressed glucagon secretion and delayed gastric emptying rather than insulinotropic effect. Only one patient had significant hypoglycemia during the single-dose study (62).

The literature regarding appropriate insulin adjustment in patients with T1DM who are using exenatide is inconclusive. Researchers have administered GLP-1 for 5 d to patients with T1DM without any reduction in their insulin dosage and a single episode of mild hypoglycemia was observed in one patient of 23 subjects. A single dose study showed that 50% reduction in meal-related insulin requirement was associated with infusion of GLP-1 (63).

Adverse effects and practical considerations. Nausea is the most common side effect and is dose dependent, can occur in 30-50% of patients as seen in adults with type 2 diabetes mellitus, although is usually transient. There is a risk of mild to moderate hypoglycemia when exenatide is used with a sulfonylurea in T2DM. Exenatide results in a moderate reduction in weight, which does not seem to be related to the adverse gastrointestinal effects. Exenatide has resulted in low levels of antiexenatide antibodies in approximately 40% of patients but had no effect on glucose control. About 6% of patients developed high antibody levels, which could result in a diminished response (64). Postmarketing cases of acute pancreatitis are reported in patients treated with exenatide including six cases of hemorrhagic and necrotizing pancreatitis. All patients required hospitalization and two deaths were reported (www.fda.gov). Exenatide and other potentially suspect drugs should be promptly discontinued and not restarted if pancreatitis is suspected. Exenatide is approved for use in adults with T2DM in conjunction with metformin or oral hypoglycemic agents. Exenatide is not approved by the Food and Drug administration approved for treatment of T1DM or use with insulin. There are no studies with use of exenatide in children. Currently, studies are underway examining the role of exenatide in T1DM in children and adults.

In conclusion, insulin replacement therapy remains the corner stone of diabetes management for patients with T1DM. Despite islet transplantation and advances in the delivery and

pharmacology of insulin, such as the development of continuous s.c. insulin infusion and rapid- and long-acting insulin analogs, many children with T1DM still fail to achieve glycemic targets. The limitations of insulin therapy with hypoglycemia and inadvertent weight gain become increasingly evident as patients approach glycemic targets.

The search for adjunctive agents in treatment of T1DM is stimulated by ongoing difficulties in safely achieving the target necessary to prevent metabolic complications in T1DM. More studies are needed to establish safety and efficacy of the above therapies in the pediatric population.

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