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Postprandial Hypoglycemia in Children after Gastric Surgery: Clinical Characterization and Pathophysiology

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Established Facts

- Dumping syndrome is a common complication in children after fundoplication, and unlike in adults, is most often characterized by postprandial hypoglycemia (PPH).
- In children with dumping syndrome, early hyperglycemia after a meal triggers an exaggerated insulin response resulting in PPH.
- In children with dumping syndrome, postprandial plasma concentrations of GLP-1 are significantly higher than in control children.

Novel Insights

- In children with PPH, antagonism of the GLP-1 receptor with exendin-(9–39) blunts the insulin response, even in the presence of hyperglycemia, suggesting that the exaggerated insulin response to a meal is at least in part due to the effects of GLP-1 on the pancreatic β-cell.
- GLP-1 receptor antagonists may represent a potential avenue for the treatment of PPH.

Key Words
Postprandial hypoglycemia · Children · Gastric surgery · Dumping · GLP-1 · Exendin-(9–39) · Insulin · Fundoplication

Abstract
Background/Aims: Dumping syndrome is a common complication in children after fundoplication and other gastric surgeries and is characterized by postprandial hypoglycemia (PPH). Children with PPH have an exaggerated GLP-1 response to a meal with an exaggerated insulin surge and subsequent hypoglycemia. We evaluated the role of GLP-1 in the pathogenesis of PPH by examining the effects of GLP-1 receptor blockade on glucose and insulin response to a meal. ***Methods:*** Six children with known PPH after surgery underwent a mixed meal tolerance test with/without the GLP-1 receptor antagonist exendin-(9–39) using an open-label crossover design. ***Results:*** Average nadir plasma glucose concentration was ≥65 mg/dl in all treatment conditions; however, 3 out of the 6 subjects had a nadir plasma

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glucose <65 mg/dl during vehicle infusion, while only 1 out of the 6 had a nadir plasma glucose <65 mg/dl during infusion of exendin-(9–39). Exendin-(9–39) suppressed postmeal insulin concentrations when compared to vehicle, with a lower peak insulin concentration observed in the children who received 500 pmol/kg/min of exendin-(9–39) (131.3 ± 125.1 pmol/l) compared to children who received 300 pmol/kg/min (231.1 ± 153.4 pmol/l) or vehicle (259.7 ± 120.2 pmol/l). Gastric emptying was not different between groups. ***Conclusion:*** Our results suggest that the exaggerated insulin response to a meal is at least in part due to the effects of GLP-1 on the pancreatic β-cell and suggest that GLP-1 receptor antagonists may represent a potential avenue of treatment for children with PPH.

Case Presentation

A 3-year-, 2-month-old male with complicated medical history noteworthy for gastric pull-through surgery for tracheoesophageal fistula (TEF) at 14 months, presented to the emergency room with a plasma glucose of 28 mg/dl associated with neuroglycopenic symptoms including confusion and dizziness following a meal. He had one prior episode of documented hypoglycemia in the setting of a prior parvovirus infection. The child had a history of 6 seizures of unclear etiology in the 2 years following TEF repair. In the emergency room, he was given an intravenous bolus of dextrose, his plasma glucose normalized, and he returned to his baseline status. Because of the history of gastric surgery and his postprandial symptoms, he was suspected to have PPH. He underwent an oral glucose tolerance test, which revealed a peak plasma glucose concentration of 351 mg/dl at 30 min and a nadir plasma glucose concentration of 41 mg/dl at 120 min postglucose load. He was started on therapy with the alpha-glucosidase inhibitor acarbose (25 mg three times/day with meals) [1]. His plasma glucose concentrations improved with acarbose treatment and dietary modifications (avoidance of simple sugars; inclusion of protein-rich foods with complex carbohydrates). Despite these therapies, he has struggled with intermittent diarrhea, a known complication of acarbose, and intermittent hypoglycemia despite treatment. Figure 1 depicts a trace of his glucose profile over a week as recorded by continuous glucose monitoring system (Medtronic® iPro™, Minneapolis, Minn., USA).

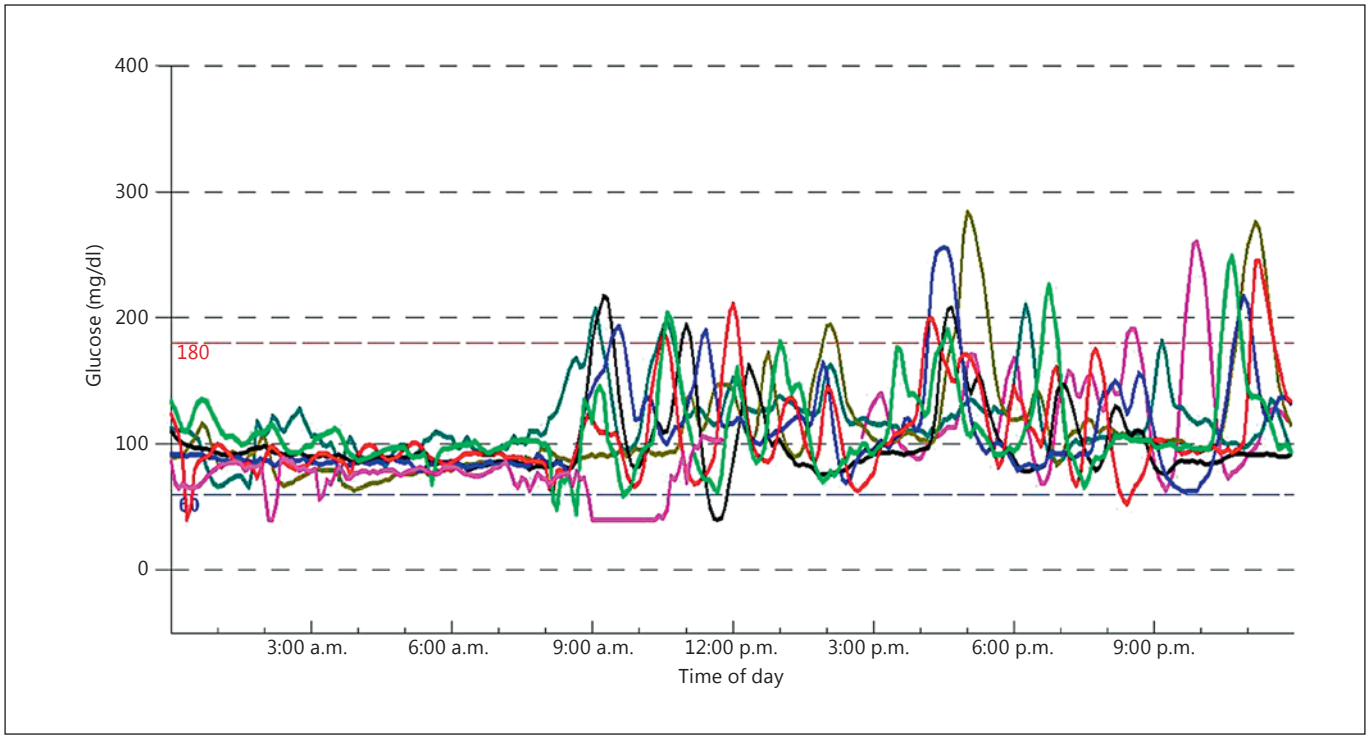
Introduction

Although described over 20 years ago [2, 3], most clinicians remain unaware of the risk of dumping syndrome (DS) after gastric surgery. In children, DS occurs more frequently as a complication of fundoplication surgery and is characterized by severe postprandial hypoglycemia (PPH), also known as 'late dumping syndrome', that typically occurs 1–3 h after a meal but without the significant gastrointestinal symptoms of 'early dumping' [1, 4].

The true prevalence of DS in children is controversial; some studies report it as an infrequent complication [5, 6], while others estimate the frequency to be higher [7, 8]. This variability may be explained by differences in the definitions of DS and screening practices used to diagnose DS. Because symptoms of PPH may not be specific, our group has advocated for universal postoperative screening to detect PPH after fundoplication [9]. Following the institution of a postoperative surveillance plan in our neonatal intensive care unit, our group has shown that 24% of children who had undergone a fundoplication showed evidence of PPH [9]. Earlier identification of PPH may lead to earlier treatment and prevention of the effects of unidentified hypoglycemic events.

The typical response to an oral glucose tolerance test or a meal in children with PPH is characterized by early hyperglycemia and an exaggerated GLP-1 response, followed by an exaggerated insulin surge and subsequent hypoglycemia [10]. The classical view of the pathophysiology has been that rapid absorption of carbohydrates following a meal results in early hyperglycemia, which triggers the exaggerated insulin response. However, peak insulin concentrations after a meal are proportionally higher than the degree of hyperglycemia in some of these children [3]. We hypothesized that the exaggerated GLP-1 response to a meal may at least in part be responsible for the postprandial hyperinsulinemia and subsequent hypoglycemia [10]. GLP-1 is a potent insulinotropic hormone secreted by intestinal L-cells after a meal. In addition to enhancing postprandial insulin secretion [11–13], GLP-1 has other actions that are complementary to the incretin effect, including inhibition of glucagon secretion [14, 15], hepatic glucose production [16, 17], gastric emptying [18, 19], and appetite [20, 21].

Under physiologic conditions, circulating plasma GLP-1 concentration is low, which has prompted speculation that circulating GLP-1 cannot fully explain the β-cell effects. However, in states where plasma GLP-1 concentrations are significantly elevated, as seen after gastric bypass surgery, the elevated concentrations are more clearly responsible for the effects on GLP-1 receptors in the β-cell [22]. In adults with PPH after gastric bypass surgery, increased GLP-1-stimulated insulin secretion has been shown to contribute significantly to the hyperinsulinemia [23] and blockade of the GLP-1 receptor by exendin-(9–39) prevents the hypoglycemia in these individuals [24]. Exendin-(9–39), a derivative of the non-mammalian peptide exendin-4, acts as a specific and



Color version available online

Fig. 1. Continuous glucose monitoring system profile for highlighted patient over the course of 1 week. Each different line represents a different day of the week. Profile shows significant daytime glucose fluctuations with significant hyperglycemia and intermittent hypoglycemia.

competitive antagonist of the GLP-1 receptor [25]. We have shown that exendin-(9–39) suppresses insulin and increases fasting plasma glucose in children and adults with congenital hyperinsulinemic hypoglycemia, and our group is currently evaluating the therapeutic potential of this peptide for this condition [26]. To examine the role of GLP-1 in the pathogenesis of PPH in children, we examined the effects of exendin-(9–39) on gastric emptying, as well as on the plasma glucose, insulin and glucagon responses to a meal in children with PPH.

Methods

Children with PPH after fundoplication or gastric surgery aged 6 months to 18 years were recruited from the Division of Endocrinology and Diabetes at The Children's Hospital of Philadelphia. The study design was an open-label randomized complete crossover. Subjects were admitted to the inpatient CTRC unit and underwent 2 experiments on 2 consecutive days after an overnight 12-hour fast. On one day, subjects received a continuous intravenous infusion of exendin-(9–39) for 1 h prior to consuming a standardized mixed meal and continued for a total of 4 h. On the other day, subjects received a continuous intravenous infusion of normal saline. At time 0, subjects consumed a mixed meal of PediaSure® (Abbott Nutrition, Columbus, Ohio, USA) 10 ml/kg (1 kcal/ml: 12% protein, 53% carbohydrate, 35% fat) by mouth or by gastrostomy tube. Because there was limited experience with exendin-(9–39) in children, we chose to start with a low dose. The first three subjects, including the subject described above, received a dose of exendin-(9–39) of 300 pmol/kg/min (0.06 mg/kg/h) [Ex-9(300)]. The dose was increased to 500 pmol/kg/min (0.1 mg/kg/h) [Ex-9(500)] in the subsequent three subjects. Acarbose was withheld in all subjects who had been treated with it. Plasma glucose concentration was measured (Siemens Rapid Point 400 Blood Gas analyzer; Siemens Healthcare Diagnostics, Deerfield, Ill., USA) at –60, 0, 10, 30, 60, 90, 120, 150, and 180 min. Plasma insulin (ELISA, ALPCO Diagnostics, Salem, N.H., USA) and glucagon (RIA, Millipore, Linco Research, St. Charles, Mo., USA) concentrations were taken at 0, 30, 60, 120 and 180 min. Plasma intact and total GLP-1 levels (ELISA, Millipore; Linco Research) were taken at 0, 10, 30, 60, 120, and 180 min. Gastric emptying was evaluated using the paracetamol method. Paracetamol (30 mg/kg) Tylenol® tablet (McNeil-PPC, Fort Washington, Pa., USA) was pulverized in a mortar and carefully mixed into the formula. The serum paracetamol concentrations were measured every 30 min using a colorimetric assay at 0, 30, 60, 90, 120, 150 and 180 min (ACET®; Vitros Chemistry Products™; Ortho Clinical Diagnostics Inc., Johnson & Johnson Health Care Systems, Piscataway, N.J., USA). The absorption of paracetamol is determined by the gastric emptying rate, and se-

Table 1. Subject characteristics

Subject	Age, years	Surgery (age at surgery)	Age at PPH diagnosis	Feeding regimen	PPH treatment	PPH frequency
1	8	Nissen fundoplication (6 months)	9 months	Oral only	Acarbose	Intermittent
2	18	Nissen fundoplication (7 months)	14 months	Both oral and gastrostomy	Feeding manipulations*	Intermittent
3	6	Gastric pull-through (13 months)	3 years	Oral only	Acarbose	Frequent
4	10	Nissen fundoplication (4 months)	3 years	Gastrostomy only	Acarbose	Intermittent
5	7	Nissen fundoplication (1 month)	2 years	Both oral and gastrostomy	Feeding manipulations*	Frequent
6	7	Nissen fundoplication (5 months)	4 years	Both oral and gastrostomy	Acarbose	Frequent

* Feedings were modified to decrease volume and slow rate of delivery.

rum concentrations correlate with gastric emptying of liquids [27]. The glycemic response is not influenced by co-ingestion of paracetamol. We measured the area under the curve (AUC) after the consumption of the formula, an accurate parameter of paracetamol absorption that is reportedly higher when gastric emptying is faster [27]. The study was approved by the Children's Hospital of Philadelphia Institutional Review Board, and informed consent was obtained from all participants or their parents.

Results

Six children aged 6–18 years (5 male) were recruited from the Division of Endocrinology and Diabetes at The Children's Hospital of Philadelphia and participated in the study (table 1). Five of the subjects had a Nissen fundoplication for severe GERD; one subject had a history of gastric pull-through surgery for TEF. All of the subjects were treated for PPH, with either acarbose or feeding manipulations prior to enrollment.

Fasting plasma glucose concentrations were 79.8 ± 3.1 mg/dl for vehicle; 83 ± 2.6 mg/dl for Ex-9(300), and 89.7 ± 10.0 mg/dl for Ex-9(500). One hour after initiation of the infusion of vehicle and exendin-(9–39) (time 0), plasma glucose was 82.2 ± 9.1 mg/dl for vehicle; 90 ± 6 mg/dl for Ex-9(300), and 89.7 ± 21.2 mg/dl for Ex-9(500). After consumption of the meal, plasma glucose concentration rose rapidly in all subjects but reached a greater peak in both exendin-(9–39) groups compared to vehicle [203.7 ± 50.5 mg/dl for vehicle; 240.3 ± 21.4 mg/dl for Ex-9(300), and 231.7 ± 23.0 mg/dl for Ex-9(500)]. Average nadir plasma glucose in all treatment conditions was greater than 65 mg/dl [66.7 ± 10.9 mg/dl for vehicle; 66.3 ± 14.5 mg/dl for Ex-9(300), and 74.3 ± 7.4 mg/dl for Ex-9(500)] (fig. 2). Three out of the 6 subjects had nadir plasma glucose <65 mg/dl during vehicle infusion, while only 1 out of the 6 had a nadir plasma glucose <65 mg/dl during infusion of exendin-(9–39) and this subject received the lower dose of exendin-(9–39). Since plasma glucose nadir occurred in all groups at 180 min after the meal, which coincided with the end of the study period, it is not known if they would have continued to fall. AUC for plasma glucose was 21,715.9 ± 3,597.8 mg · min/dl for vehicle; 22,192.5 ± 4,784.7 mg · min/dl for Ex-9(300), and 25,207.1 ± 1,157.5 mg · min/dl for Ex-9(500).

At time 0, plasma insulin concentrations were undetectable for the vehicle and low exendin-(9–39) treatment conditions and 6.5 ± 3.3 pmol/l for the high exendin-(9–39) dose. After a mixed meal, plasma insulin concentration increased in all subjects, reaching a peak at 30 min postmeal. Peak insulin concentration was lower in the high exendin-(9–39) dose group [259.7 ± 120.2 pmol/l for vehicle; 231.1 ± 153.4 pmol/l for Ex-9(300), and 131.3 ± 125.1 pmol/l for Ex-9(500)]. By 120 min postmeal, plasma insulin concentration was still elevated in the vehicle treatment group, while it was suppressed in both exendin-(9–39) groups [87.8 ± 107.7 pmol/l for vehicle; 17.9 ± 20.8 pmol/l for Ex-9(300), and 20.8 ± 19.5 pmol/l for Ex-9(500)]. By 180 min postmeal, insulin concentration returned to baseline in all groups (fig. 3). AUC for insulin was 19,435.4 ± 10,392.6 pmol · min/l for vehicle; 14,695.85 ± 12,662.9 pmol · min/l for Ex-9(300), and 9,058.5 ± 7,562.7 pmol · min/l for Ex-9(500).

At time 0, plasma glucagon concentration was higher in the Ex-9(500) treatment group [60.3 ± 22.1 pg/ml for vehicle; 52 ± 12.1 pg/ml for Ex-9(300), and 74.7 ± 8.5 pg/ml for Ex-9(500)]. Plasma glucagon concentrations were higher in the Ex-9(500) group throughout the study with peak concentrations in all groups at 30 min postmeal [114 ± 50.1 pg/ml for vehicle; 127.5 ± 75.7 pg/ml for Ex-9(300), and 145.7 ± 33.6 pg/ml for Ex-9(500)].

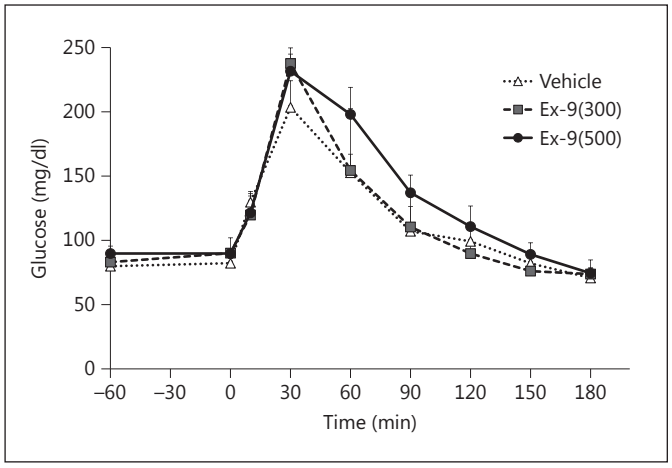


Fig. 2. Mean blood glucose concentration ± SEM after a mixed meal during vehicle (triangle, dotted line), Ex-9(300) (square, dashed line), and Ex-9(500) (circle, solid line) infusion.

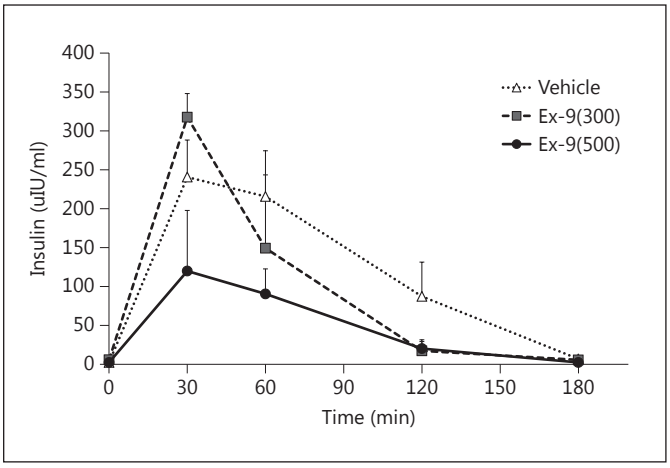


Fig. 3. Mean plasma insulin concentration ± SEM after a mixed meal during vehicle (triangle, dotted line), Ex-9(300) (square, dashed line), and Ex-9(500) (circle, solid line) infusion.

After 60 min of vehicle/exendin-(9–39) infusion (time 0), plasma intact GLP-1 concentration was slightly higher under the vehicle condition [9.4 ± 14.9 pmol/l for vehicle; 3.1 ± 1.8 pmol/l for Ex-9(300), and 3.7 ± 2.3 pmol/l for Ex-9(500)]. Intact GLP-1 peaked 30 min after the meal [72.8 ± 26.1 pmol/l for vehicle; 65.8 ± 33.3 pmol/l for Ex-9(300), and 75.2 ± 5.8 pmol/l for Ex-9(500)] (fig. 4). A similar pattern was seen for total GLP-1 (data not shown).

The effect of exendin-(9–39) on gastric emptying was examined using the acetaminophen method. AUC for acetaminophen plasma levels were not different among the groups suggesting that exendin-(9–39) did not significantly alter gastric emptying during the study. AUC for acetaminophen was 3,436.6 ± 465.2 μg · min/l for vehicle; 3,387.5 ± 898 μg · min/l for Ex-9(300), and 3,742.8 ± 124.3 μg · min/ml for Ex-9(500).

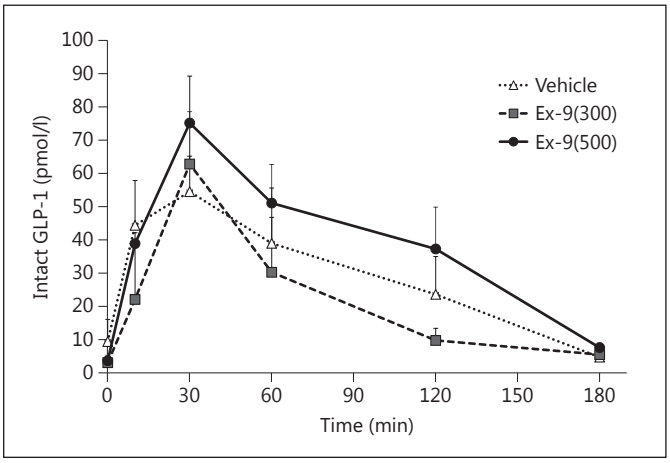


Fig. 4. Mean plasma intact GLP-1 concentration ± SEM after a mixed meal during vehicle (triangle, dotted line), Ex-9(300) (square, dashed line), and Ex-9(500) (circle, solid line) infusion.

Discussion

Our results suggest that the exaggerated insulin response to a meal seen in children with PPH after gastric surgery is at least in part due to the effects of GLP-1 on the pancreatic β-cell, as the blockade of the GLP-1 receptor with exendin-(9–39) blunted the insulin response even in the presence of hyperglycemia. A larger study including more subjects would be necessary to establish the statistical significance of these observations.

The major limitation of our study, in addition to the small sample size, relates to the fact that none of the subjects experienced significant hypoglycemia during the 3-hour postmeal experimental period. It is not uncommon for episodes of late dumping after meals to be intermittent, so perhaps an oral glucose tolerance test would have been more appropriate as an experimental approach to reliably elicit PPH. While it is possible that at the time of recruitment the PPH had resolved in these children, the high plasma insulin concentration in response to the meal strongly argues against that conclusion. For safety reasons, we were limited on the dose of exendin-(9–39)

that we could use in the study. However, it is clear from our limited data that the higher dose of exendin-(9–39) is more effective in inhibiting the exaggerated insulin response to a meal. In normal individuals, a dose of 300 pmol/kg/min exendin-(9–39) abolishes the effects of physiologic postprandial plasma levels of GLP-1 but not of supraphysiologic levels [25, 28]. Thus, it is not surprising that a higher dose is required to block the effects of supraphysiologic levels of GLP-1 previously reported in children with PPH after fundoplication and observed in this study.

Despite these limitations, our work provides insights into the contribution of GLP-1 to the pathophysiology of this condition. Similarly, in adults with PPH after gastric bypass surgery, Salehi et al. [23, 24] showed that exendin-(9–39) inhibits the exaggerated insulin response and prevented hypoglycemia in individuals with PPH after gastric bypass surgery. These findings suggest that GLP-1 contributes significantly to the hyperinsulinemia and subsequent hypoglycemia, and strongly support the GLP-1 receptor as a potential target for treatment of PPH after gastric surgery. This is an important consideration as current treatment options for children with PPH remain limited and suboptimal. A variety of therapies have been used with varying success, including uncooked cornstarch [29], pectin [8], octreotide [30], acarbose [3], and changes to the composition, volume, and rate of administration of feedings [31]. Many of the affected children continue to have severe hypoglycemia despite these interventions and require a regimen of continuous enteral feedings but continue to be at high risk of hypoglycemic events if feedings are abruptly stopped.

Close monitoring of postprandial glucose excursions is essential for preventing episodes of severe hypoglycemia that can cause neurologic damage. Our standard practice for home monitoring is to have parents monitor plasma glucose concentrations using a handheld glucose meter twice daily 90 min after meals or at other times if symptoms of hypoglycemia are noted. Recognizing the limitations of this strategy, continuous glucose monitoring systems may be used to provide increased monitoring capacity of glycemic excursions in those treated for PPH after fundoplication [32–34]. In our population, several patients have successfully worn the Medtronic® iPro™ to monitor glycemic control of PPH for a period of 3–7 days to assess their glycemic control.

Conclusions

PPH remains a largely unrecognized complication of fundoplication and other gastric surgeries. While the exact incidence is unknown, many children will not have symptoms of PPH, and we strongly advocate for universal screening in the immediate postoperative period in at-risk children. Early detection can lead to earlier treatment and prevention of brain damage from severe hypoglycemia. However, current treatment options, including acarbose, remain limited and have side effects, and despite these measures, many children will continue to have persistent PPH and may require continuous feeds or feeding manipulations. Our data show that blockade of the GLP-1 receptor can blunt the insulin surge seen in children with PPH and implicates GLP-1 in this exaggerated insulin response. The possibility of new targeted therapies to decrease the effects of GLP-1 may improve the management of these children in the future.

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