ORIGINAL ARTICLE

Possible Ways to Improve Postprandial Glucose Control in Type 1 Diabetes

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Introduction

THE DIABETES CONTROL AND COMPLICATIONS TRIAL and subsequent Epidemiology of Diabetes Interventions and Complications trial have unequivocally established that intensive glucose control significantly reduces microvascular and macrovascular long-term diabetes complications in those with type 1 diabetes (T1D).^{1–3} The improvement in diabetes control was, however, associated with a threefold increase in severe hypoglycemia events, which in many cases result in additional calorie consumption, intentional hyperglycemia, limited insulin titration, and weight gain.⁴

Glucose control, as measured by HbA_{1c}, is widely accepted as the hallmark measure of mean blood glucose (MBG), and is derived from a composite of fasting plasma glucose (FPG) and postprandial glucose (PPG) exposure. The exact role of postprandial hyperglycemia, and how it relates to glycated hemoglobin (HbA_{1c}) are debatable.^{5–9} Some studies have shown a significant relationship of PPG with HbA_{1c} more than FPG,^{9,10} whereas other studies suggested the contrary.^{11,12} Postprandial hyperglycemia contributes significantly to overall glycemic burden and represents one of two key targets along with fasting glucose control for improvement in MBG.

One of the greatest challenges and unmet needs in diabetes management is limitations in effectively and consistently controlling postprandial hyperglycemia.³ Increased PPG levels have been significantly associated with increased healthcare resource utilization, including visits, calls, e-mails to healthcare providers, and overnight hospitalizations among adults with diabetes that use multiple daily injections (MDI).¹³ A measurement of plasma glucose (by self-monitored blood glucose—SMBG) 2 h after the start of a meal has commonly been recommended and has been a key indicator of postprandial hyperglycemia.¹⁴ At present, however, there is no international consensus for either the recommended measurement

or specific targets for PPG levels for patients with diabetes. Current recommendations are neither well established nor consistently individualized for individuals with T1D; however, the recommended 2-h PPG level <140 mg/dL has been suggested by the American Association of Clinical Endocrinologists (AACE); while values <180 mg/dL have been put forth by the American Diabetes Association (ADA), targets of <160–180 mg/dL were recommended by European Association for the Study of Diabetes (EASD), and <160 mg/dL was the suggested target provided by International Diabetes Federation, all targeting these values with no increase in associated rates of significant hypoglycemia.¹³

Importance of PPG Control

A significant correlation has been observed between postprandial hyperglycemia and elevated intraocular pressure,¹⁵ cognitive dysfunction,¹⁶ oxidative stress, and many other conditions—with these data generally obtained in retrospective studies.¹⁷ The Framingham Offspring Study and the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study showed a relationship between postprandial hyperglycemia and cardiovascular disease.^{18,19} The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial has shown that decreasing postprandial hyperglycemia may reduce the incidence of new cardiovascular events in people with impaired glucose tolerance.²⁰ However, the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study²¹ and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study²² failed to show beneficial effects of lowering PPG.²³ A post hoc analysis of the data from the HEART2D study concluded a lower risk of

cardiovascular events with prandial versus basal insulin therapy in a subgroup of older individuals with type 2 diabetes (T2D) and prior acute myocardial infarction, despite similar HbA_{1c} between the two groups.²⁴ No well-controlled, randomized study to date has carefully assessed the impact of PPG excursions on rates of complications or outcomes in T1D.

In contrast, at this time, there is no definitive evidence for the precise relationship between PPG excursions and the development and progression of microvascular and macrovascular complications of diabetes.^{17,25} The ability to draw conclusions from long-term trials with head-to-head comparisons is difficult due to the absence of an ideal therapeutic agent that would only decrease PPG effectively and have a negligible effect on FPG.¹⁷ Difficulties in comparing trials to date are also due to limitations in study design, endpoints, and the methods of analysis employed.¹⁷

Contributors to Postprandial Hyperglycemia

The absorption of carbohydrates in the upper gastrointestinal (GI) tract results in increases in plasma glucose concentrations, which usually starts about 10–20 min after the start of a meal, but this effect can vary significantly based on a number of factors, including, meal composition, duration of diabetes, presence of autonomic dysfunction, and alterations in microbiota of the upper GI tract.^{26,27} In an individual without diabetes, plasma glucose peaks in ~60 min after the start of a typical meal and rarely exceeds 140 mg/dL, usually returning to normal levels within 2 to 3 h.¹⁴ The corresponding physiologic release of insulin coincides with meal ingestion and is stimulated by glucose (and free fatty acids) with both a rapid increase in insulin concentrations and onset of insulin action within the first 30–120 min after the meal. This response generally controls the significant increase in blood glucose in healthy individuals, regardless of the carbohydrate load consumed since patients with T1D have little or no residual beta cell function after 2 to 3 years following diagnosis (which is in contrast to T2D, where postprandial hyperglycemia is the consequence of both inadequate meal-related insulin release and failure to suppress ongoing hepatic glucose production). However, in both scenarios, rapid prandial insulin effect that can mimic the time action profile of physiological insulin may be desirable in efforts to better control the meal-related excursions in glucose.

As noted previously, postprandial hyperglycemia in T1D is multifactorial, and in addition to the factors already discussed, individuals with T1D also have a postprandial paradoxical rise in glucagon (although lesser in magnitude to that seen in T2D), and PPG is impacted by timing, quantity, and composition of the meal, mismatch of meal absorption with exogenous insulin absorption and action (often maximal more than 1 to 2 h after injection), and patient-related causes such as reduced or skipped mealtime insulin dose or challenges with accuracy in estimating total carbohydrate intake.^{14,28–30}

Carbohydrate counting has been shown to be an important determining factor of postprandial hypoglycemia and hyperglycemia.³¹ More recently, continuous glucose monitor (CGM) data revealed the PPG patterns in T1D, including rapid glucose spikes with high glycemic index carbohydrates and late postprandial hyperglycemia with increases in dietary fat and protein.^{32–36} High-fat meals may alter gastric emptying, often contributing to late blood glucose elevations that can occur as

late as 4 to 5 h after the meal,^{32,33} and can increase free fatty acid levels that impair insulin sensitivity, and further contribute to higher glucose values.³⁵ Higher protein intake has also been shown to increase PPG levels 3–5 h postmeal.^{32,37} A high-fat and high-protein meal consisting of similar amounts of carbohydrates require more insulin to lower PPG when compared with low-fat, low-protein meals in T1D.³⁸

There are also data to suggest that food order has a significant role to play. A study showed that when protein and fat were consumed 15 min before carbohydrates, the mean PPG levels were lower by 28.6%, 36.7%, and 16.8% at 30, 60, and 120 min, respectively.³⁹ The glycemic index of food may also affect PPG levels, as foods with a high glycemic index have been shown to result in even greater and more rapid increase in blood glucose following a meal. On the other hand, those foods with a lower glycemic index result in lesser fluctuations in blood glucose.^{40,41} One other key variable—namely the specific timing of the subcutaneous insulin dose—in relation to the meal has been shown to be an important factor in PPG control.^{32,33}

A recent review concluded that injecting rapid-acting insulin analogs (RAIA; e.g., lispro, aspart, and glulisine) 15–20 min premeal results in ~30% lower PPG levels and lower reported rates of postmeal hypoglycemia when premeal glucose levels are in range.³⁶ Postprandial administration of RAIA is a less effective method of controlling PPG levels and may increase a significant risk of hypoglycemia and increased glucose variability.³⁶

Therapeutic approaches for T1D management during exercise also need to account for the residual effects of meals, insulin dose, and the impact of activity on glucose turnover, insulin mobilization, glucagon, and sympathetic response.⁴² Several types of exercises are associated with rapid reductions in glucose (walking and jogging), while other forms of exercises may result in rapid increase in plasma glucose (weight training and high-intensity intervals).⁴² Duration and type of exercise must also be considered in preventing exercise-induced hypoglycemia and postexercise hyperglycemia.⁴³ The Dose Adjustment For Normal Eating (DAFNE) trial showed that dietary training with flexible insulin dosing improved diabetes outcomes and quality of life, and was cost-effective.^{44,45} The dietary changes recommended in the DAFNE trial persisted for 6 months and glycemic control was maintained up to 7 years.^{46,47}

Gastroparesis is a relatively uncommon long-term complication in poorly controlled patients with diabetes. Patients with gastroparesis may have delayed glucose absorption, thus resulting in a delayed rise in PPG.⁴⁸ Rarely, patients with gastroparesis may also have rapid absorption of food intake. The use of insulin pumps has been shown to improve PPG better than subjects using MDI.⁴⁹

Therapeutic Options to Address Prandial Glucose Control

Many new basal insulin analogs such as insulin detemir, glargine (U100 and U300), and degludec (U100 and U200), or the use of insulin pumps has allowed effective control of FPG, most without increasing nocturnal hypoglycemia.^{50–54} In late March, the Food and Drug Administration (FDA) approved specific changes in wording for the use of insulin degludec based on results from the DEVOTE trial that reported reduced rates of severe hypoglycemia.⁵⁵

Mealtime human soluble (regular) insulin (in contrast to porcine/bovine regular insulin) has been used since 1992 in an effort to control PPG. More recently, RAIAs (insulin lispro, glulisine, and aspart) have generally replaced human regular insulin in individuals with T1D as they are dosed closer to mealtime and have been shown to have a more rapid pharmacokinetic (PK) and pharmacodynamic (PD) response.⁵⁶ The RAIAs have a more rapid onset of action, earlier and higher peak activity with a shorter duration of action than human regular insulin.⁵⁶ However, RAIAs are still recommended for dosing 15–30 before meals and are known to have significant insulin effect more than 2 h after injection—which many consider inadequate to achieve optimal PPG control.^{56–58}

Faster acting insulin aspart (Fasp) is a new formulation of insulin aspart that includes two additional formulation excipients, L-arginine and niacinamide. L-arginine serves as a stabilizing agent and the addition of niacinamide promotes a more rapid formation of insulin monomers after subcutaneous injection, facilitating more rapid absorption across the endothelium into the circulation.⁵⁹ The pooled analysis of PK and PD studies that compared Fasp versus insulin aspart showed an ~5 min earlier onset of first appearance of insulin (4 vs. 9 min), an approximately two times higher early insulin exposure, and a 74% greater early glucose-lowering effect for Fasp versus insulin aspart.⁵⁶ A Japanese study confirmed similar findings.⁶⁰ Offset of exposure and glucose-lowering effect occurred 12–14 min earlier with Fasp than insulin aspart.⁵⁶

The Onset 1 registration trial at 26 weeks showed not only noninferiority of Fasp in terms of HbA_{1c} compared to insulin aspart, but also superiority for PPG excursions (21.21 mg/dL and 12.01 mg/dL decrease at 1 and 2 h, respectively) without increased risk of hypoglycemia in patients with T1D.⁵⁸ At 52 weeks in the same trial, overall glycemic control had significantly improved with Fasp versus insulin aspart, consistent with the 26-week study findings.⁵⁷ A projection analysis that used the Onset 1 trial data showed that Fasp can reduce healthcare-related costs up to £1,715 in England.⁶¹ Fasp also improved glucose control in the registration Onsets 2 and 3 trials in patients with T2D.^{59,62} Currently, Fasp is not currently approved for use in insulin pumps used in the United States. In a recent 6-week small study for pump compatibility, no microscopically confirmed infusion-set occlusions were observed for Fasp.⁶³

Glucagon-like peptide (GLP-1) is an incretin hormone secreted by intestinal L cells in response to food intake and works on suppressing postprandial glucagon release, increasing (on demand) insulin secretion (a mechanism not possible in patients with T1D due to general absence of beta-cell insulin release), increasing satiety, and delaying gastric emptying.^{30,64} Currently, none of the GLP-1 analogs is approved by the FDA to be used in T1D. Shorter-acting GLP-1 analogs have been shown to improve glucose control with associated reductions in insulin dose compared to placebo; however, long-acting GLP-1 analogs have shown to be less consistent as adjunctive therapy for glucose control in patients with T1D.⁶⁵ In small studies, exenatide improved PPG in patients with T1D.^{66,67} Liraglutide did not demonstrate significantly greater effects on PPG control in patients with T1D.^{65,68} While improvement in HbA_{1c} was observed, the changes were small in magnitude—although also associated with modest weight loss. Overall, the studies showed a significant increase in the risk of DKA and severe hypoglycemia

in ADJUNCT 1 and 2 trials in T1D.^{69,70} As a result of these data, the developer of liraglutide officially announced that it would not pursue a new drug application (NDA) to the FDA or European Medicine Agency (EMA) for use of liraglutide for T1D as adjunctive therapy.

Pramlintide is an analog hormone to human amylin—a peptide synthesized in the pancreatic beta-cells and co-secreted with insulin. Pramlintide has been approved for adjunctive use in insulin-treated individuals with both T1D and T2D—and exerts its clinical effects by means of increases in satiety, a delay in gastric emptying, and reducing postprandial plasma glucagon concentrations.⁷¹ Premeal injections of pramlintide decreased glucose excursions for the first 2 h following a mixed meal by suppressing postprandial glucagon concentrations in a randomized crossover study.⁷¹ The time to peak blood glucose was also significantly slower with pramlintide.⁷¹ It has been shown that regardless of the duration of diabetes, patients achieved a significantly lower HbA_{1c} and weight loss; however, patients with increased duration of diabetes had significantly more adverse effects, including increased rates of nausea/vomiting and a higher risk of hypoglycemia.⁷² Another recent study compared pramlintide with liraglutide in patients with T1D in a closed-loop system without premeal bolus insulin administration. Pramlintide suppressed postmeal glucagon levels and lowered hyperglycemia.⁷³ There is an ongoing study (NCT01269047) that compares exenatide and pramlintide in patients with T1D for PPG control.⁶⁵

The only FDA-approved adjunctive therapy for T1D is pramlintide; however, its clinical use is limited due to a number of factors, including the need for significant adjustment in insulin dose in many individuals, treatment-limiting significant side effects such as nausea, vomiting, and decreased food intake in some individuals, and increased rates of hypoglycemia, as well as the higher cost of therapy.²⁹ Pramlintide and GLP-1 analogs delay gastric emptying, and thus may help in delaying the absorption of glucose matching with the action of RAIA.

The SGLT2 inhibitors lower blood glucose through inhibition of renal glucose reabsorption in the proximal tubule of the kidney, whereas SGLT1 inhibition delays the absorption of glucose from the upper GI tract, thus blunting PPG.^{74,75} Sotagliflozin (dual SGLT1 and SGLT2 inhibitor) and dapagliflozin (selective SGLT2 inhibitor) have shown improved glucose control in patients with T1D in recently published randomized, controlled, double-blind studies.^{76–78} However, none of the SGLT (sodium–glucose cotransporter) inhibitors is FDA or EMA approved for clinical use in patients with T1D.

Inhaled insulin has been studied in several forms in an effort to utilize an alternate delivery method (pulmonary absorption) to alter PK/PD of mealtime insulin, while the earlier attempts at pulmonary insulin were generally unsuccessful due to low bioavailability (Exubera®) and limited improvement in time action profile, technology using fumaryl diketopiperazine (the excipient representing an essential part of Technosphere insulin [TI]) for pulmonary delivery of insulin (TI, Afrezza®; Mannkind, Westlake Village, CA). TI had demonstrated even more rapid onset of action compared to the RAIA insulin lispro.⁷⁹ TI appears in the blood in <1 min, thought to be due, in great part, to the extent of pulmonary alveolar space available for insulin absorption and due to the rapid dissolution of the insulin delivery particles.⁸⁰ TI also results in more rapid and higher

peak action.⁸¹ In addition, a study of subjects with T2D has shown more rapid suppression of endogenous glucose production with TI at doses of 24 and 16 U compared to lispro 10 U.⁸²

Recently, data were provided to the U.S. FDA that resulted in changes in labeling language for TI that support the observation of the first measurable insulin effect that occurs in ~12 min, and peak effect is noted ~35–45 min after dosing with a return to baseline insulin effect levels after ~1.5–3 h.⁸³ Based on the PD, in these studies, the dose of TI required to achieve a similar glucose effect based on glucose infusion rate has been modified to at least 1.5 times the usual dose of subcutaneously injected RAIA. Whether this is the result of formulation properties, pulmonary delivery, or other changes in insulin action or clearance is not known. However, dosing (as an example) for a patient currently utilizing 8 U of RAIA may require 12 U of TI as an initial dose to achieve the similar glucose-lowering effect.⁸⁴ This dosing recommendation is further supported by analysis of the doses of TI ultimately utilized to achieve similar glucose control in the randomized clinical trials comparing TI to RAIAs where equivalent dose ratios approximating 1.5–2 times dose of TI to RAIA were reported after 12 or more weeks of titration.^{85–87}

TI was shown (by design) to achieve a noninferior reduction in HbA_{1c} when compared to RAIA in registration trials in those with T1D. This noninferiority was achieved with significantly less reported hypoglycemia and lesser weight gain compared to the use of RAIA.⁸⁵ Additional studies confirmed reduced hypoglycemia—an outcome that is, in part, attributed to its rapid “on and off” insulin action with TI.^{85,88–90} The PD profile reported confers a faster onset and shorter duration of action that may permit more rapid postprandial insulin action that coincides with the rates of glucose absorption after meals.⁸⁰ A simulation study using modeled data from TI clinical trials suggested that higher doses of TI premeal or split dosing premeal and postmeal of TI may provide improved PPG profile with lesser fluctuations in postmeal glucose than conventional treatment with subcutaneously administered rapid-acting insulin products, and would be likely to do so without increasing the risk of hypoglycemia.⁹¹

In current clinical use, there are higher rates of reported “underdosing” of TI as documented by lesser clinical effect when 1:1 mealtime insulin dose conversion is used. However, with additional clinical experience, patients and healthcare providers have been advised to consider the higher dose conversion when switching between RAIA and TI, and appropriate titration may allow for more aggressive and higher dosing of TI when clinically indicated.⁸⁴ TI has a significantly shorter duration of action and different time action profile compared to RAIA, and for many individuals may require a modified approach to both initiation and titration as well as supplemental dosing 1–3 h postmeal (by inhalation) to achieve the optimal clinical effect. Similarly, with shorter mealtime insulin action following TI inhalation, individual patients may also need to alter (generally increase) their basal insulin dose.

A small number of individual reports have identified those who have used TI for PPG control with the hybrid closed-loop (HCL) pump therapy. Given the short duration of action of inhaled TI with meals, and the flexibility of basal adjustments with HCL, some individuals report clinical improvement, although this is not currently an indicated use of TI. However, using TI with HCL system will not account for the total daily

insulin dose and thus many patients may experience higher fasting glucose values, and usually not recommended.

A small ($n=15$) pilot feasibility single-arm study using TI showed a decrease in HbA_{1c} in 6 weeks.⁹² An investigator-led collaborative open-label, multicenter randomized pilot study (Study Comparing Prandial Insulin Aspart vs. Technosphere Insulin in Patients with Type 1 Diabetes on MDI- or STAT Study) compared TI with insulin aspart effects on PPG control and postprandial time in range (TIR) for 0–4 h postmeal using CGM data. The STAT study showed that PPG was significantly lower at 1 and 2 h postprandial with TI compared to insulin aspart.^{89,90} In the per-protocol analysis (with additional postprandial TI dose), mean glucose values and postprandial TIR significantly improved compared to insulin aspart.^{89,90} Details of the STAT study results will be presented at the 2018 ADA and EASD annual meetings in Orlando, FL, and Berlin, Germany, respectively^{89,90} (data on file with BDC).

Due to the rising cost of insulin, biosimilar insulins are also now being developed as an alternative to the established branded RAIA.^{93–95} Similar PK/PD results have been demonstrated with biosimilar lispro versus insulin lispro in use.⁹⁶ A crossover study that compared biosimilar lispro and insulin lispro in use for pump compatibility and safety found similar results for infusion set occlusions, hypersensitivity reactions, and hypoglycemia events.⁹⁷ In T1D and T2D, similar efficacy and safety were found in the SORELLA 1 and SORELLA 2 studies, respectively.^{98,99} Similar immunogenicity profiles were found between biosimilar lispro and insulin lispro in use in the SORELLA 1 and SORELLA 2 studies.¹⁰⁰ Earlier PK/PD studies with biosimilar (follow-on) insulin aspart also showed similar profiles to insulin aspart. Phase 3 clinical trials in T1D and T2D (GEMELLI studies) are ongoing in the United States and Europe for biosimilar insulin aspart approvals (NCT03211858) with the FDA and EMA.¹⁰¹

BioChaperone insulin lispro has also been developed to enable the acceleration of insulin absorption. It had previously demonstrated an accelerated insulin action profile across multiple phase 1 and 2 studies in people with T1D and T2D compared to insulin lispro.^{102–104} A trial (NCT03179332) that compared PK/PD properties of BioChaperone insulin lispro in insulin pumps with insulin aspart and Flasp recently showed superior results according to a press release by Adocia, Inc. (Lyon, France).¹⁰⁵ Eli Lilly & Co, Inc. (Indianapolis, IN) recently completed the recruitment for the phases 2 to 3 trials for ultra-rapid-acting insulin lispro for MDI and continuous subcutaneous insulin infusion (CSII) (NCT03056456 and NCT02703350).¹⁰⁴ Results from early phase studies of this compound supported faster time action profile than insulin lispro, although full results of phase 3 studies are not currently available.^{106,107}

Some other alternative methods have been tried to increase insulin absorption. Insulin co-injected with hyaluronidase to increase insulin absorption may be a promising alternative for PPG management.^{108–110} Despite favorable results, the company (Halozyme, Inc., San Diego, CA) discontinued development of their product, given both the clinical and regulatory requirements necessary to complete the NDA for the FDA. Investigational devices that apply local heat have been found to increase insulin absorption and thus reduce PPG.^{111–114} Whether such approaches will achieve improved PPG remains to be determined.

Conclusion

The recent availability of HCL systems (artificial pancreas or AP systems) to deliver insulin in response to CGM recorded glucose data and specific insulin administration algorithms have been reported, and demonstrate significant reductions in fasting glucose in many trials.^{52,54} However, control of PPG continues to remain a clinical challenge as it requires patient input of proper carbohydrate intake and current insulin action profiles may be limited to respond to rapid increases and decreases in PPG even with the HCL system. CSII or pumps are currently only used in <1% of insulin-requiring patients, so the generalizability of such therapy remains to be determined.

Identification of optimal basal and prandial insulin therapies that better mimic normal physiology and utilize rapid and frequent glucose measurement that can facilitate/help patients manage their diabetes at the moment is needed for more effective management. There also remain ongoing efforts to identify a “SMART” (glucose sensing) insulin that alleviates the need for multiple insulin types and may eliminate the need for advanced pump technologies. One such approach uses boronate-based glucose sensing (that is attached to the insulin molecules) for continuous sensing.^{115,116}

Effective PPG control still requires multiple daily efforts that include, but are not limited to the following: proper and accurate assessment of carbohydrate intake (DAFNE trial), food composition, insulin dose adjustments based on physical activity, current glucose level (as measured by SMBG), or real-time CGM.³⁰ CGM data allow patients and healthcare providers real-time feedback to control PPG more effectively.^{117–119} Patients using insulin pumps may bolus with different options (standard, square wave, modified combination, and dual wave) to improve PPG control, especially in patients with gastroparesis.^{120–122} Development of ultra-RAIA and proper use of very rapid-acting pulmonary insulin such as TI can assist a number of patients in their effort to improve PPG. Until another very rapid-acting prandial insulin is available, appropriate use of currently available insulins (aspart, lispro, glulisine, Flasp, and Technosphere Insulin) along with glucose monitoring (SMBG/CGM) should be considered the standard of care to mitigate/reduce PPG elevations and excursions.

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