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Optimizing Postprandial Glucose Management in Adults With Insulin-Requiring Diabetes: Report and Recommendations

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Faster-acting insulins, new noninsulin drug classes, more flexible insulin-delivery systems, and improved continuous glucose monitoring devices offer unprecedented opportunities to improve postprandial glucose (PPG) management and overall care for adults with insulin-treated diabetes. These developments led the Endocrine Society to convene a working panel of diabetes experts in December 2018 to assess the current state of PPG management, identify innovative ways to improve self-management and quality of life, and align best practices to current and emerging treatment and monitoring options. Drawing on current research and collective clinical experience, we considered the following issues for the ~200 million adults worldwide with type 1 and insulin-requiring type 2 diabetes: (i) the role of PPG management in reducing the risk of diabetes complications; (ii) barriers preventing effective PPG management; (iii) strategies to reduce PPG excursions and improve patient quality of life; and (iv) education and clinical tools to support endocrinologists in improving PPG management. We concluded that managing PPG to minimize or prevent diabetes-related complications will require elucidating fundamental questions about optimal ways to quantify and clinically assess the metabolic dysregulation and consequences of the abnormal postprandial state in diabetes and recommend research strategies to address these questions. We also identified practical strategies and tools that are already available to reduce barriers to effective PPG management, optimize use of new and emerging clinical tools, and improve patient self-management and quality of life.

Freeform/Key Words: diabetes, diabetes technology, insulin therapy, postprandial excursions, PPG

Abbreviations: A1c, hemoglobin A1c; ADA, American Diabetes Association; BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; GV, glucose variability; MDI, multiple daily insulin; PPG, postprandial glucose; PPH, postprandial hyperglycemia; QOL, quality of life; SGLT2, sodium-glucose cotransporter type 2; T1D, type 1 diabetes; T2D, type 2 diabetes.

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The relationship between poorly controlled glycemia and both macrovascular and microvascular complications of diabetes is well established. Until recently, management efforts have focused on lowering hemoglobin A1c (A1c) levels, with most targeting fasting plasma glucose (FPG). In 2001, however, an American Diabetes Association (ADA) consensus meeting established postprandial glucose (PPG) as a potentially distinct contributor to both A1c targets and diabetes-related complications [1]. Subsequent evidence suggests that reducing PPG excursions may be equally or more important than reducing FPG in achieving overall A1c goals and in reducing risk of diabetes-related complications [2, 3]

Despite these developments, managing PPG remains one of the most challenging aspects of diabetes care [4, 5]. An important advance occurred in 2014, with the International Diabetes Federation having issued specific guidelines on treating and assessing PPG excursions in patients with diabetes [6]. However, to date, few patients with insulin-requiring diabetes report satisfaction with available management strategies or clinical support tools [6, 7], and few spend adequate time in their target blood glucose (BG) range [8]. Meanwhile, many questions raised by the ADA consensus statement remain unanswered, including the relative contributions of FPG and PPG to A1c and long-term complications, and ways in which PPG excursions impact patients' time-in-range (defined as 70 to 180 mg/dL), self-management, and quality of life (QOL) [9].

Faster-acting insulins, new noninsulin drug classes, more flexible insulin-delivery systems, and improved continuous glucose monitoring (CGM) devices offer unprecedented opportunities to improve PPG management and overall care for people with insulin-treated diabetes, as well as new opportunities to understand and target PPG excursions specifically [10]. For these reasons, the Endocrine Society convened a working panel of diabetes experts in Washington, DC on 15 December 2018 to assess the state of PPG management, align best practices to current and emerging treatment and monitoring options, and identify innovative ways to address PPG management to improve self-management and QOL for the ~200 million adults worldwide with insulin-requiring diabetes [11]. This patient population includes 30 million people with type 1 diabetes (T1D), including 1 million on pump therapy worldwide [12]. The remainder are people with advanced type 2 diabetes (T2D) or other forms of insulin deficiency [13, 14].

Our discussion, summarized below, drew on current research and collective clinical experience to address the following issues and develop recommendations for adults with insulin-requiring diabetes:

- Knowledge needed to define optimal PPG guidelines and goals
- Ways that improving PPG management can reduce risks of diabetes complications
- Barriers preventing effective PPG management
- Strategies to reduce PPG excursions and improve patient QOL
- Education and clinical tools to support endocrinologists managing PPG

1. PPG Dynamics and Biology

Overall glycemia results from the sum of basal and PPG exposure. CGM studies have provided a clear understanding of the dynamics of postmeal BG control in healthy individuals, with PPG peaking ~30 to 60 minutes after a meal starts, with maximum levels <140 mg/dL. BG levels generally normalize to preprandial levels after 2 to 3 hours, although it can take 5 to 6 hours after a meal for complete absorption of ingested carbohydrates [15–17]. The primary factors determining PPG profile are: (i) insulin secretion, (ii) insulin action in stimulating glucose uptake and suppressing glucose production, (iii) glucagon suppression, (iv) glucose effectiveness in stimulating its own uptake and production, and (v) gastric emptying and incretin hormones. Defects in many of these five factors can underlie postprandial hyperglycemia (PPH) in prediabetes and overt diabetes [18–23]. For patients with diabetes, the size, composition, and timing of meals, preprandial glycemic level, comorbidities, and duration and type of diabetes may also modulate this relatively complex network [24–28].

2. Current Understanding of the Clinical and QOL Impact of PPG Excursions

A. Clinical Data

PPG excursions may include both hyperglycemia and hypoglycemia. Hypoglycemia remains a significant risk when prandial insulin is used to control PPG and can have multiple indirect effects on glucose variability (GV) [29]. An important research and clinical focus has been cardiovascular disease (CVD) effects of hypoglycemia such as arrhythmias, ECG changes, adverse cardiovascular events, and mortality, as well as considerable patient distress [30, 31]. Fear of further hypoglycemia may lower adherence to recommended insulin and sometimes other therapies, setting up a vicious cycle requiring higher insulin doses accompanied by "defensive eating" and weight gain [32]. Although such marked clinical and psychological impact can potentially make hypoglycemia the limiting factor in achieving postprandial goals, most outcome studies of PPG excursions have focused on PPH. Several epidemiologic studies have shown a correlation between elevated postprandial BG values and negative clinical outcomes, with the strongest being studies linking PPH in pregnancy to macrosomia [33, 34] and population data supporting a relationship between PPH and CVD [35]. However, the precise impact of PPH on diabetes-related complications remains unclear. Evidence showing the impact of hyperglycemic excursions on nuclear cytokines and other markers of oxidative stress and inflammation provide a cellular rationale for the distinctive contribution of PPH.

To date, only a few clinical trials suggest that managing PPG excursions measurably impacts diabetes-related complications, notably a large study involving Australian adolescents with T1D that associated multi-injection insulin programs or pump therapy with improved A1C and PPG levels along with reduced appearance of diabetic retinopathy [36]. In contrast, the HEART-2D trial compared prandial to basal insulin therapy 21 days after acute myocardial infarctions in persons with T2D and found lower daily mean PPG with prandial insulin, but no associated practical or biological impact on A1c or cardiovascular events [37]. Additionally, clinical data are conflicted over the contribution of PPG to overall glycemia at varying levels of A1c [38, 39].

B. Impact on QOL

Patients commonly attribute a diverse array of experiences to PPH, all included under the umbrella term of QOL. These experiences include impaired well-being, negative mood changes, disruptive life events (*e.g.*, impaired sleep quality and fatigue), and disease-specific impacts (*e.g.*, diabetes distress) over both the long and short term. Patients with insulin-requiring diabetes frequently report PPH episodes, saying they feel "miserable," "sluggish," or "foggy-brained." Concerns about both PPH and hypoglycemia are common in patients using bolus insulin, as is frustration at readings that suggest failure to balance dietary choices and/or physical activity with insulin intake [40]. Perceptions that blood sugar is too high after meals can themselves exacerbate diabetes distress, fueling fear, anxiety, shame, or hopelessness about the ability to manage BG. CGM is changing these dynamics by reducing underdosing and overdosing concerns, but creating new anxieties when mealtime BG is not adequately controlled despite best efforts.

Published studies about the relationship between PPH and the myriad experiences and physical and cognitive symptoms lumped together as QOL are generally small, anecdotal, and inconsistent, making it difficult to determine the extent and impact of any given factor. Additionally, differences in diabetes type, diabetes duration, treatment modality, personality, age, and comorbidities complicate head-to-head comparisons, as do varying definitions of PPH and GV [41–45]. Studies of long-term impact of PPH on cognitive decline and dementia are somewhat stronger. Rizzo *et al.* [46], for example, found a strong association between mean amplitude glycemic excursions and global cognitive function in elderly adults with T2D using CGM. Whether these results reflect PPG specifically is unclear, as is the

direction of association. Other findings associating glucose peaks to dementia risk in people with diabetes suggest a more direct link and the possibility of intervention [47].

3. Managing PPG Excursions

A. Lifestyle Modification

Patients who want to reduce or limit medication use with lifestyle interventions often find existing options such as very low–calorie diets to be unrealistic or unsustainable [48, 49]. Severely carbohydrate-restricted diets can rapidly affect BG, but long-term efficacy remains unclear, and risks of hyperglycemia and hypoglycemia can complicate treatment, especially when combined with intensive exercise. In insulin-requiring diabetes, unawareness that high-fat/high-protein foods need adequate insulin despite low carbohydrates may undermine glycemic control [50, 51]. Additionally, many patients report being unable to follow ADA exercise guidelines, often citing lack of time for 30 minutes of activity at least 5 days a week [52, 53].

Potentially more achievable but equally effective lifestyle and behavioral tools may provide viable alternatives (Table 1 [54–66]). Preliminary data suggest that simply eating carbohydrates last in a meal may more effectively regulate PPG and lower glucose excursions. Three small studies, two involving T2D and the other prediabetes, found that eating protein and/or vegetables first, followed 10 minutes later by carbohydrates, significantly reduced both glucose and incremental glucose peaks compared with eating carbohydrates first or eating all components together [54–56]. A study in children with T1D found that eating protein and fat 15 minutes before carbohydrates lowered PPG and GV significantly more than standard meals [57]. Evidence grounded in the physiology of circadian rhythms suggests that exclusively limiting food intake to a 6- to 8-hour daily window (a common recommendation is 10:00 AM to 6:00 PM) may benefit body weight and cardiovascular health regardless of macronutrients or portion sizes [67]. Several nutritional supplements, including viscous fiber, ascorbic acid (vitamin C), and apple cider vinegar also appear to reduce postmeal glucose levels [59, 60].

Some evidence also suggests that timing of exercise may be equally if not more important than its amount or vigor [61]. One small study found that in non–insulin-using people with T2D, 10 minutes or more of postprandial walking may lower the glycemic effect of evening meals more than premeal exercise, effectively blunting PPG excursions [62]. Other studies have shown similar benefits from moderate or high-intensity exercise 30 minutes to an hour after eating [63].

B. Pharmacologic Management

Faster-acting insulins more closely mimicking physiologic action of endogenously secreted insulin may improve PPG control. In late 2017, the US Food and Drug Administration approved fast-acting insulin aspart (Fiasp) for both T1D and T2D, with a 4.5-fold greater insulin exposure in the first 15 minutes than aspart insulin but comparable time to maximum concentration and total exposure, along with a greater glucose-lowering effect during the first 90 minutes [68, 69]. Clinical studies on T1D show modest improvement in A1c and PPG over conventional aspart, with peak impact 1 hour after eating [70]. These findings, as well as the potential benefits of faster acting insulin aspart in pump therapy, deserve further investigation.

Technosphere inhaled insulin also has a considerably faster absorption profile than do conventional rapid-acting insulin analogs and improves PPG more effectively at 1 and 2 hours along with less late hypoglycemia when dosed appropriately. Although some patients prefer the pulmonary formulation, optimal dosing can be challenging, and, as with all faster acting insulins, cost limits usage. A study in T1D showed modest improvements over insulin aspart in glucose control with accompanying weight loss, findings that deserve further study [71]. Several ultra–rapid-acting insulins are in clinical development with even faster and

Table 1. Lifestyle and Nutrition Approaches to Minimize Postprandial Excursions

Approach	Recommendation	Explanation and Potential Impact on PPG
Monitor PPG	Monitor BG at 1 h and/or 2 h after meals by fingerstick or CGM	Increasing BG monitoring after meals (especially larger meals) will provide insight into the need for a correction dose of rapid-acting insulin. High-fat meals delay stomach emptying and result in a later timing of peak PPG values [58].
Take insulin before eating	Leave enough time for insulin to start working ("lag time") before eating. This is typically 20 min for analog insulins, but considerably less with newer ultra–rapid-acting insulins and/or if BG is well controlled.	Taking insulin up to 30 min before meals with analog insulin is more effective and potentially safer in controlling mealtime PPG than taking insulin right at, or after, meals, a practice that can promote insulin stacking if the person becomes frustrated with initially high BG [64–66].
Carbohydrates last	Eat nonstarchy vegetables and protein (*e.g.*, fish, meat) first. Save carbohydrates and starchy foods, including starchy vegetables (*e.g.*, potatoes, peas, yams), for last.	Several small studies of patients with either T1D or T2D show that eating protein and vegetables first reduces both PPG and incremental glucose peaks significantly more than eating carbohydrates first or eating all components together [54–57].
Add supplements	Consider taking vitamin C and fiber supplements and adding apple cider vinegar to meals.	Taking 500 mg of vitamin C (ascorbic acid) twice daily has been shown to improve PPG [60]. Viscous fibers, present in oat bran, citrus fruits, and guar gum, β-glucan, and psyllium supplements have also been found to reduce postmeal sugars. Apple cider vinegar, one teaspoon right before meals, can reduce PPG, which is likely related to acetic acid and the slowing stomach emptying [59]. As vitamin C and vinegar are acidic, brushing teeth is wise.
Exercise after eating	Exercise moderately for 10 to 20 min within an hour of eating. Moderate activity may include brisk walking, using exercise machines, or lifting light weights. If using insulin or sulfonylureas with tightly controlled BG, adjust the dose down with the guidance of your provider.	A small study shows at least 10 min of walking after an evening meal may blunt PPG excursions more than premeal exercise [62]. Other studies show similar benefits from moderate or high-intensity exercise 30 minutes to an hour after eating [61, 63].

This table lists promising lifestyle and nutritional approaches to managing PPG that providers can suggest with T1D or insulin-requiring T2D. Although evidence of efficacy and underlying mechanisms remains limited, these easy-to-follow, low-cost, and low-risk approaches may be useful alternatives to less practical or sustainable dietary and exercise regimens.

shorter action profiles that more closely mimic the physiology of endogenously secreted insulin, both for subcutaneous administration as well as oral/buccal, nasal, and pulmonary routes, although most are unlikely to be available for another 5 to 10 years [72, 73].

Pramlintide, a synthetic form of amylin, has long been known to reduce PPG excursions in adults with insulin-requiring diabetes. However, high risks of gastrointestinal side effects and hypoglycemia, especially in T1D, limit clinical utility [74–77]. Although GLP-1 analogs are widely recognized as helpful in glycemic and weight control in patients with T2D using basal insulin, randomized controlled trials of patients with T1D show neither consistent nor sustained A1c reductions, with higher risks of severe hypoglycemia or diabetic ketoacidosis (DKA). However, in both ADJUNCT ONE and TWO, liraglutide's effects on glycemic control were significantly better in C-peptide–positive patients compared with patients with undetectable C-peptide, a finding deserving additional consideration [78, 79].

Several recently completed phase 3 trials suggest that sodium-glucose cotransporter type 2 (SGLT2) inhibitors, commonly used as second-line therapies in T2D, improve both fasting and postprandial glycemic control along with lowering blood pressure and weight loss without increasing hypoglycemia in inadequately controlled T1D, although with an increased DKA risk to 4% to 5% [80–82]. Recently completed phase 3 trials associated the investigational dual-inhibitor combination drug sotagliflozin with sustained A1c reduction, weight loss, lower insulin dose, improved patient-reported outcomes, and fewer episodes of severe hypoglycemia when combined with optimized insulin therapy in T1D, particularly in patients with A1c levels <7.0%. Risk of DKA was significant, as with other SGLT2 inhibitors [82, 83]. Regulatory approval of these agents for use as an oral adjunct to adjustable insulin in adults with T1D varies by country, with none currently approved for this use in the United States.

4. Current and Emerging Management Technologies

A. CGM

By providing dynamic, real-time measures, CGM systems have contributed greatly to understanding PPG excursions along with overall patterns of glycemia. CGM systems measure interstitial glucose concentration to provide wearers with real-time glucose readings and trend arrows indicating the direction and rate at which glucose values change. By providing this information in the context of historical data, CGM systems give wearers and their healthcare providers insight into current and retrospective trends. Patients using a CGM system can see directly how and when different meal types, behaviors, exercise, and medications affect PPG and adjust insulin timing and dose by combining glucose readings and trend arrow data with insight into the time required for insulin absorption. CGM data also provide information to patients about the impact of insulin timing relative to meal ingestion, improving the potential to reduce both PPH and delayed hypoglycemia with postmeal dosing [64–66, 84, 85]. Studies of persons with type 1 diabetes using CGM have shown they spend more time-in-range than do those receiving usual care, reducing both hyperglycemia and hypoglycemia, and decreasing GV [86–88]. Improved glycemic control has also been shown in T2D [58].

The ability to analyze real-time data is a key advantage of CGM systems, expanding patient and clinician understanding of glucose fluctuations, height and duration of PPG excursions, and specific PPG profiles, as well as facilitating comparisons with normal glucose physiology. CGM also makes it easier to predict effects of temporary changes in glucose values on weekends vs weekdays or associated with events such as menses, viral infections, or short courses of steroids. By depicting effects of different meal types on PPG, CGM data have also highlighted the need to consider dietary composition and quantity when counseling patients and, in particular, to consider protein and fat as well as carbohydrate intake in dosing calculations [50, 51, 89, 90]. This approach marks a revolutionary change in prandial management, requiring a more holistic understanding of nutrition, gastrointestinal absorption, and insulin kinetics and action and opening the possibility of targeted interventions personalized to factors including time of day, type of meal, physical activity, and stressors.

Managing the quantity and variety of information these devices provide remains challenging for both patients on insulin pump or multiple daily insulin (MDI) therapy and their providers, however. We suggest that providers consider a stepped approach to reviewing and interpreting reports, focusing on data sufficiency, CGM use, time-in-range, and GV, as well as ambulatory glucose profile and daily view [91]. Patients may require even more guidance than their providers in interpreting data, as well as in using trend arrow data safely and practically [92, 93], making certified diabetes educators who can demonstrate new devices and help patients interpret CGM more valuable than ever [94].

B. Continuous Subcutaneous Insulin Infusion

Continuous subcutaneous insulin infusion (CSII, or insulin pump) therapy aims to mimic normal insulin secretion by continuously infusing rapid-acting insulin at preselected rates,

with patient-activated bolus doses at mealtimes or as corrections for hyperglycemia. Besides bolus dose calculators that consider carbohydrate intake, current glucose concentration with glucose target, and insulin on board, some devices include presets for different meal sizes, and most provide options to extend insulin delivery over a specified time for high-protein or high-fat meals or for patients with gastroparesis who require extending the prandial insulin dose to match delayed digestion and food absorption.

Current and emerging CSII systems have considerably improved CGM integration and insulin delivery options. A key advance has been low-glucose suspend and predictive low-glucose suspend features that stop insulin delivery when glucose levels rapidly approach or fall below a threshold level for hypoglycemia, for a preset period of time (2 hours with low-glucose suspend), or with predictive low-glucose suspend until there is an increased glucose trajectory as determined by the integrated CGM so the glucose level rises above the low glucose threshold. Also important are hybrid closed-loop systems that automatically adjust basal rates based on sensor readings but currently require patients to enter carbohydrate intake manually for insulin boluses. Sophisticated downloads through CGM systems provide data on glucose trends, including time in target range as well as hyperglycemia and hypoglycemia, glucose measurements by capillary testing, timing of insulin doses, and basal rate changes, which help refine both insulin doses and patient behaviors. Reports provided by CGM systems, such as daily or overlay reports, are providing new insight into an array of "diabetes behavior pitfalls" that increase risks of hypoglycemia, PPH, or rapid, unpredictable fluctuations between them [95–97], including insulin dosing during or after meals, inaccurate carbohydrate counting, neglecting effects of protein and fat intake, overreliance on postmeal correction doses, holding or delaying insulin doses for near-normal BG before a meal, and multiple small corrective insulin boluses. Such problematic dosing behaviors remain the biggest challenge to optimal PPG levels, even with hybrid closed-loop pumps. Fully automated closed-loop systems (artificial pancreases), the technologic answer (together with better ultra–fast-acting insulins) to normalizing glucose, are being tested, but for the foreseeable future insulin dosing still requires careful analysis of BG patterns by clinician and patient to determine guidelines for optimal decision making.

Despite CGM and increasingly sophisticated device features, dosing inconsistencies and errors remain common. Current dosing algorithms rely on carbohydrate intake and sensor or capillary glucose, but they do not fully account for many of the myriad factors that influence PPG and ultimately GV. Dosing calculations neglect food composition, trend arrows, medications, biological and emotional stressors, activity, environmental factors, and timing of insulin delivery. Patients therefore may not see expected results from premeal insulin doses, even when calculated correctly. Assumptions about active insulin time, insulin sensitivity, carbohydrate ratios, timing of eating, and adjunctive noninsulin medications can also skew calculations. Our long-term expectation is that dose calculators and decision support systems will continue evolving to become more sophisticated and accurate using artificial intelligence systems that learn a patient's glucose responsiveness, and they will remain a key element of intensive insulin treatment programs for many years. The ultimate goal is highly sophisticated closed-loop dosing algorithms that remove the need for human input in basal and prandial insulin dosing, although we expect that there will be considerable discussion and scientific analysis to determine what patients will most benefit from this expensive and advanced technology.

5. Needs and Recommendations

A. Defining Optimal PPG Guidelines and Goals

Lack of a consistent, practical, cost-effective, and accurate measure of PPG complicates the assessment of clinical trials and, ultimately, effective management. Most studies of PPG or PPH consider the impact of A1c or glycemic variability rather than that of sustained hyperglycemia causing oxidative stress, which may be a more direct measure of the impact of

glucose fluctuations [98]. Studies of PPH specifically also fail to capture hypoglycemic pathologies such as inflammation, arrhythmias, and coagulopathies as contributors to GV. Some studies measure glucose levels 2 hours, others 1 hour, after a meal. One metric gaining traction is the biomarker 1,5-anhydroglucitol (GlycoMark®), which has been negatively associated with macrosomia and other negative outcomes in CVD and in women with T1D, T2D, or gestational diabetes [33, 35]. The role of biomarkers in research will likely continue to evolve with CGM and other new measurement technologies.

Assigning maximum allowable values at a single point in time to a process occurring over several hours limits the usefulness of current guidelines in assessing and optimizing postmeal BG control. Without proven dynamic parameters, intervention trials must use nonrigorous surrogate measures of PPG such as nonphysiologic meal or carbohydrate challenges. CGM may help refine definitions of PPH and establish tolerable limits, although we must still establish any added benefit of focusing on time-in-range in the postprandial state vs the full 24-hour period, and determine ideal parameters for postmeal time-in-range along with the impact of factors such as diabetes type and duration, dietary composition and timing, ethnicity, and pharmaceuticals. Fully differentiating the impact of basal vs bolus interventions will require sophisticated wider-ranging measures than BG alone, such as circulating metabolites and biomarkers/mediators of cellular stress or damage, especially in the postmeal state. Given these limitations, the committee thought that there is insufficient evidence to advocate any specific criteria for optimal PPG control. Toward these ends, we recommend rigorous CGM studies in well-characterized groups to address these issues:

- Identify optimal measurement methodology for clinical practice and research, establishing clear clinical definitions, goals, and relative predictive power for GV, PPH, and delta and/or aggregate rises in prandial BG via short-term correlations and surrogate outcomes (markers of oxidative stress and inflammation) as well as long-term "hard" outcomes (adjudicated cardiovascular events or other end-organ complications).
- Identify an integrated definition of a healthy, nontoxic postprandial state that combines BG with an extensive characterization of circulating metabolites, biomarkers, cytokines, and novel factors.

B. PPH Management and Risks of Diabetes Complications

Determining the value of PPG control in minimizing diabetes-related complications was perhaps the most important question we considered. Despite clear evidence that PPH exacerbates oxidative stress and inflammation, it remains unclear whether controlling these glycemic spikes affects the development or progression of microvascular or macrovascular disease above that attributed to overall glycemia. Also, although our discussion was focused on persons with insulin-requiring diabetes receiving intensive insulin programs, we expect that the consequences of PPH will be similar regardless of the diabetes type and treatment. Addressing this critical issue will require research based on innovative strategies that selectively vary PPG values without A1c-based BG differences. A related issue is the importance of PPG control for preserving β-cell function in newly diagnosed T1D. The Diabetes Control and Complications Trial showed that MDI injections or CSII pump therapy preserved C-peptide secretion better than standard therapy [99]. Given the potential for PPG spikes to activate inflammation, we need studies to differentiate PPG control from overall BG control in recent-onset T1D.

We also discussed the need to identify patient subgroups most amenable to specific interventions, particularly given today's faster-acting and safer insulins and CGM. Uncovering predictive markers for better PPG responses to specific pharmacological or lifestyle interventions is becoming increasingly important in an era of personalized medicine. Studies of intense PPG management vs standard control in persons at high risk for PPH-related morbidity or mortality are particularly needed, with an expectation that these can be rapidly translated into clinical practice. Patients receiving hematopoietic stem cell transplantation, for

example, often experience severe PPH due to high-dose steroids [100], but the value of treating PPH in this population to reduce infectious complications and mortality remains unexplored. To address these questions, we recommend both short-term studies with surrogate markers and long-term studies with adjudicated outcomes to:

- Clarify PPH's contribution to A1c and diabetes complications.
- Confirm that using CGM and best available intervention strategies to control PPG reduces onset and/or progression of complications.
- Determine the value of intensive PPG control in preserving C-peptide in recent-onset T1D.
- Compare the impact of intense vs standard PPG control in people at high risk for PPH-related morbidity or mortality.

C. Elucidating the Relationship Between PPG and QOL

Improving QOL will require using quantifiable measures to develop a more sophisticated understanding of the relationship between PPG and GV on patients' perceptions that make up what is commonly termed QOL. Pressing research needs include determining how excessive, lengthy, or frequent PPH must be to affect QOL, as well elucidating the effects of postmeal hypoglycemia. A particularly timely topic that worries many patients is how peak or sustained hyperglycemia or hypoglycemia impacts the risk for dementia/cognitive decline. Building the knowledge base and awareness of these issues will require behavioral and pharmacological intervention studies to measure more meaningful physical and emotional outcomes than simply "patient satisfaction," including fear of hypoglycemia, insecurity about managing glycemic changes, and concerns about dosing accurately. We specifically recommend clinical intervention studies that:

- Include relevant and standardized QOL measures of emotional and physical outcomes.
- Identify whether sustained PPH vs rapid changes in glycemia up or down most affect QOL.
- Clarify the relationship between postmeal hyperglycemia and hypoglycemia on quantifiable and clinically understandable QOL parameters, and confirm the clinical predictive power of current assessment tools.
- Confirm the association between QOL and PPG control by showing that intervention trials designed for better and more predictable postmeal BG control improve QOL parameters, and, conversely, that specific QOL interventions are associated with improved PPG control.

D. Strategies to Reduce PPG Excursions

Safe, effective, and practical intervention strategies remain a pressing need in managing PPG. Although providers and patients usually expect these to be medications, we recommend a closer look at a new array of behavioral and dietary options meshing with patient requests for lifestyle and nutritional approaches to minimize medications, cost, and complexity. Clinicians can describe these behavioral options using relatively simple messages that empower patients, particularly when coupled with CGM. We also support continued efforts to develop novel approaches to optimizing PPG control such as faster and smarter prandial insulins along with exploring noninsulin pharmacological agents as adjunctive therapy, and alternative insulin delivery (*e.g.*, pulmonary) when dosed appropriately. Rigorous, carefully designed and monitored trials are recommended to:

- Identify effective sustainable dietary and lifestyle approaches as adjunct therapy in insulin-treated patients, elucidating underlying mechanisms and monitoring relevant clinical outcomes, including weight and lipid control and BG predictability, together with PPG.
- Compare the value of several behavioral options in a stepwise fashion vs a single intervention.
- Critically examine current faster-acting insulins to identify patient characteristics, and dosing and timing strategies, to optimize clinical benefits.

- Determine long-term safety and best practices for using inhaled insulin.
- Continue searching for an ideal prandial insulin matching the kinetics of endogenous prandial insulin, focusing on safety, efficacy, and meaningful clinical benefits.
- Determine cardiovascular and renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists in T1D, with particular emphasis on clarifying strategies to limit DKA risk.
- Analyze the safety and efficacy of GLP-1 agents as adjunctive therapy in C-peptide–positive patients with T1D.

E. Optimizing Use of Clinical Tools to Improve Self-Management

As new and emerging technologies change day-to-day management decisions, clinicians must provide substantial guidance in using them, including advanced training in pump use, interpreting CGM data, and personalizing dosing instruction to include behavioral, dietary, and exercise choices. Current CGM-regulated and nonautomated CSII systems demand a focus on correct timing and dosing of bolus insulin. Trend arrow data, although a great advance, can be overwhelmingly complex. In a move toward standardization, the Endocrine Society recently convened two expert panels to develop approaches to adjusting rapid-acting insulin doses for adults treated by MDI injections or nonautomated CSII using trend arrows, based on individual insulin sensitivity and trend arrow direction [92, 93]. Many new tools and phone apps are also in development or becoming available to improve self-management skills for meal choice, calorie and carbohydrate counting, activity level, bolus adjustments, and other self-care behaviors. Automated decision-support systems and "virtual coaches" using artificial intelligence to analyze CGM data allow patients to visualize effects of insulin dosing, eating patterns, and physical activity in real time, enabling them to make both medical and behavioral adjustments accordingly. Also of considerable interest are "smart pens" that can track injection data, calculate doses, and share therapy data with caregivers and health-care providers. We recommend the following steps to optimize patient and provider knowledge about and use of these developing clinical tools:

- Provide access to CGM therapy to every patient with insulin-requiring diabetes on insulin pump or MDI therapy, along with a standardized education program to optimize analysis and utilization of trend arrows and other data.
- Continue developing advanced algorithms for "bolus calculators" that account for trend arrows, macronutrient intake beyond carbohydrates, physical activity, and timing of insulin delivery, incorporating inexpensive and accessible clinical decision-support devices and phone apps.

6. Discussion

Managing PPG to minimize or prevent diabetes-related complications will require a deeper understanding of fundamental questions about quantifying and clinically assessing the metabolic dysregulation and other consequences of the abnormal postprandial state. We particularly need more rigorously defined parameters for successful PPG management, including a maximum allowable PPG value and the precise time to measure it. Growing use of CGM should allow us to base more useful goals on proven healthy criteria for time-in-range or aggregate BG in the postprandial period. However, doing so will require extensive research into what BG number or range, and at what frequency and over which length of time, is associated with biologic damage and complications, and how factors such as disease type, disease duration, meal size, meal composition, meal timing, or ethnicity affect these measures. We also must examine the effects of circulating lipids, amino acids, other metabolites, and inflammatory factors in the postprandial state. Although we identified several promising behavioral strategies that may have immediate clinical value, defining effective and sustainable clinical strategies and tools for healthy PPG management calls for substantial research addressing these basic questions.

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