

Postprandial Glycaemic Excursions: Implications for Health and Effects of Non-pharmacological Interventions

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Chairperson:	Bo Ahrén ¹
Speakers:	Louis Monnier, ² Bo Ahrén
	1. Lund University, Sweden 2. University of Montpellier, France
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Meeting Summary

‘The Ominous Quartet’ represents four glycaemic disorders at the centre of cardiovascular diseases in diabetes, including ambient hyperglycaemia, glycaemic variability (GV), postprandial glucose (PPG) excursions, and hypoglycaemic episodes. It is important to understand the interrelationship between these disorders, targets and thresholds for monitoring purposes, and impact on cardiovascular outcomes. Louis Monnier’s talk focused on PPG and GV. There is evidence that PPG excursions are responsible for adverse outcomes. GV could be responsible for adverse outcomes as short-term GV is strongly associated with the occurrence of hypoglycaemic episodes, which in turn leads to adverse outcomes. Therefore, both PPG excursions and GV should be targeted by therapeutic interventions. Pharmacological treatment can reduce PPG excursions by delaying gastric emptying, diminishing hepatic glucose output through reducing glucagon, and reducing glucose absorption from the gut. However, as it is important to reduce both the duration and magnitude of PPG excursions, non-pharmacological interventions are also required to achieve recommended targets. Bo Ahrén focused on non-pharmaceutical interventions for PPG management, particularly the use of whey protein (WP).

Health Risks Associated with Elevated Postprandial Glucose or Increased Glycaemic Variability

Louis Monnier

Monnier, University of Montpellier, France, opened his talk by mentioning ‘The Ominous Quartet’: four glycaemic disorders at the centre of cardiovascular diseases in diabetes. These include chronic/ambient hyperglycaemia, GV, PPG excursions, and hypoglycaemic episodes. Ambient hyperglycaemia and hypoglycaemia have a proven negative impact on cardiovascular outcomes.¹⁻⁴ A 1% reduction in haemoglobin A1c (HbA1c), a marker of sustained glucose exposure, results in a 20% reduction in cardiovascular disease risk. Hypoglycaemia enhances platelet aggregation and has pro-arrhythmic effects. However, whether PPG excursions and GV result in adverse outcomes requires further discussion. Monnier also emphasised the importance of defining thresholds and targets in these glycaemic disorders for monitoring and control purposes. For ambient hyperglycaemia, HbA1c should be <7% and time in range >70%. The alert threshold for hypoglycaemia has been defined at 70 mg/dL by the International Hypoglycaemia Study Group (IHSG), with significant hypoglycaemia recorded at <54 mg/dL.^{5,6} Threshold and targets for GV and PPG excursions are less clear.

Postprandial Hyperglycaemic Excursions

In healthy individuals, the absorption of carbohydrates following a meal results in an increase in blood glucose, which is tightly controlled by the insulin response and reduction in glucagon secretion. This period, termed the postprandial state, lasts 4–5 hours, followed by the post-absorptive period, which lasts for 6–8 hours, during which blood glucose levels are maintained at a near-normal level by the hydrolysis of glycogen stored in the liver. In the fasting state, defined as 10 hours after meal consumption, the liver produces glucose from lactate and alanine through gluconeogenesis to maintain glucose levels. Monnier noted that an individual spends “half of the time in the postprandial state and only 2 hours in the fasting state at the end of the

nocturnal period, emphasising the importance of the postprandial state.”⁷

The degree of insulin secretion, insulin sensitivity, and metabolic consequences differ between individuals with normoglycaemia, impaired glucose tolerance (IGT), and Type 2 diabetes. In healthy individuals, relative insulin secretion is 80–100% compared with 50–80% and <50% in those with impaired glucose tolerance and Type 2 diabetes, respectively. Consequently, insulin sensitivity decreases while insulin resistance increases, both in the liver and peripherally, causing a diminished hepatic insulin sensitivity and sustained overproduction of glucose that ultimately presents as fasting and postprandial hyperglycaemia and Type 2 diabetes. It has been demonstrated that in normoglycaemia, peak glucose concentration occurs 30 minutes after a meal compared with 60–120 minutes in Type 2 diabetes.⁸ Furthermore, evidence indicates that peak postprandial glucose usually occurs after breakfast as hepatic glucose production is governed by the circadian rhythm and is at its maximum at the time of breakfast.^{9,10} Thus, the ideal timepoint to check postprandial glycaemia in patients with diabetes is 1–2 hours post-breakfast.

The threshold for defining PPG excursions is important. A strong correlation is evident between HbA1c and peak post-breakfast glucose, where an HbA1c of 7% corresponds to a peak post-breakfast glucose value of approximately 160 mg/dL.⁹ Thus, maintaining an HbA1c <7% can help reduce the peak post-breakfast glucose to <160 mg/dL, the threshold recommended by the International Diabetes Federation (IDF). Reducing the peak post-breakfast glucose to <180 mg/dL, the threshold recommended by the American Diabetes Association (ADA), only ensures HbA1c levels <7.5%. Monnier noted that “the IDF recommendation may be preferable as it ensures an HbA1c below 7%.”

PPG excursions may be responsible for adverse outcomes; Ceriello et al.¹¹ demonstrated a direct correlation between postprandial hyperglycaemia and production of nitrotyrosine, a marker of oxidative stress and contributor to the development of complications in Type 2 diabetes. Additionally, the absolute impact of postprandial glucose to HbA1c remained constant at approximately 1% across all

non-insulin-treated subjects with Type 2 diabetes and an HbA1c ≥ 6.8 .¹² Thus, highlighting that PPG is the main contributor to overall hyperglycaemia in well-controlled subjects with Type 2 diabetes, whereas fasting hyperglycaemia is the primary contributor in individuals with advanced and poorly controlled Type 2 diabetes.¹³

Also under debate is the relationship between PPG excursions and GV. A strong positive correlation has been demonstrated between changes in PPG excursions (areas above preprandial glucose values [AUC_{pp}]) and changes in GV (mean amplitude of glycaemic excursion [MAGE]) from baseline to after 8 weeks of treatment with gliptins in patients with Type 2 diabetes ($R^2=0.48$; $p<0.001$), implicating that approximately 50% of GV is due to the PPG.¹³

Glycaemic Variability

Monnier discussed two main types of GV: short- and long-term variability. Short-term variability can be divided into two components: within-day and between-day glucose variability. The %GV (standard deviation of glucose/mean glucose) represents the best metric for evaluating GV. A %GV of 36% is the most suitable threshold to distinguish between stable and unstable glycaemia in diabetes.¹⁴ Other metrics exist for estimating GV; however, Monnier noted that “most other metrics are too complex for clinical practice.”

Whether GV has a role in adverse outcomes remains questionable. A strong correlation is evident between MAGE and the urinary excretion rate of isoprostanes, a marker of the activation of oxidative stress.¹⁵ This implies that, at minimum, GV is associated with the activation of oxidative stress, a key player in diabetes complications. This was confirmed by Ceriello et al.,¹⁶ who determined that fluctuations in blood glucose correlate to fluctuations in nitrotyrosine, another indicator of oxidative stress. Despite these indications, Monnier stated that “we have no strong evidence that GV is responsible for adverse outcomes.” Numerous studies have, however, indicated that high GV is associated with risk of hypoglycaemic episodes.^{14,17} Thus, there is an indirect relationship between GV and adverse outcomes, as hypoglycaemic episodes are responsible for adverse outcomes.

Therapeutic Implications

Monnier went on to discuss the therapeutic implications and emphasised that both PPG excursions and GV are equally important to reduce HbA1c, MAGE, and AUC_{pp}, as evidenced when individuals with Type 2 diabetes were treated with a combination of dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin.¹³ However, there are limitations with pharmacological agents. For example, the implementation of a basal insulin regimen in Type 2 diabetes results in a downward shift in the 24-hour glycaemic profile without any improvement in GV. Monnier noted the importance of reducing both the duration and magnitude of PPG excursions, which would also require non-pharmacological interventions.

In summary, while numerous conclusions can be made regarding the interrelationship between optimum blood glucose targets and impact on outcomes of the ominous quartet of glycaemic disorders, the IDF recommends PPG excursions be <160 mg/dL and measured after breakfast. With respect to short-term GV, Monnier et al.¹⁸ demonstrated that %GV should be $<36\%$ and that 50% of GV is explained by PPG excursions. There is evidence that PPG excursions are responsible for adverse outcomes, but it is predominantly short-term GV that has been strongly associated with the occurrence of hypoglycaemic episodes and in turn leads to adverse outcomes. Non-pharmacological interventions are the first-line measures for controlling excessively high PPG excursions and GV. Pharmacological interventions can be further implemented when non-pharmacological interventions are insufficient. Non-pharmacological interventions must be added when pharmacological therapies have been used first and failed to achieve the recommended PPG excursions and GV targets.

Nonpharmacological Interventions for Postprandial Glucose Management

Bo Ahrén

Importance of Managing Postprandial Glucose in Type 2 Diabetes

Ahrén, Lund University, Sweden, opened his talk by highlighting the clinical importance of PPG and the subsequent need to develop therapeutic interventions to target this problem. He underscored the findings by Monnier et al.¹⁸ demonstrating that in individuals with Type 2 diabetes treated with oral anti-hyperglycaemic agents alone and with an HbA1c <7.3%, the relative contributions of PPG and fasting plasma glucose (FPG) to HbA1c were >60% and <40%, respectively.¹⁸ This emphasises the importance of targeting PPG with therapy to reduce HbA1c.¹⁸ Furthermore, a prospective intervention trial found that only 64% of patients with FPG <5.5 mmol/L had an HbA1c <7%.¹⁹ In contrast, 94% of patients with PPG <7.8 mmol/L had an HbA1c <7%. Decreases in PPG accounted for nearly twice as much of the reduction in HbA1c as did decreases in FPG. Thus, control of fasting hyperglycaemia is not sufficient for good glycaemic control, with control of postprandial hyperglycaemia essential for achieving recommended HbA1c goals.

Pharmacological Management of High Postprandial Glucose

Ahrén reiterated the importance of targeting both peak PPG after meal ingestion and duration of elevated PPG. PPG excursions can be managed by reducing overall glycaemia, specifically by delayed gastric emptying, reduced hepatic glucagon secretion, and decreased glucose absorption from the gut. Current medications target all the aforementioned approaches.

Glucagon-like peptide 1 (GLP-1) is a gut hormone that stimulates insulin secretion, inhibits glucagon secretion, delays gastric emptying, and reduces appetite. These effects together result in a reduction in FPG, PPG, and body weight. The reduction in PPG is achieved by reducing hepatic glucose outputs through inhibition of glucagon secretion together with a delay in gastric emptying.²⁰ GLP-1 forms the basis for

incretin therapy (i.e., GLP-1 receptor agonists and DPP-4 inhibitors). The latter prevents the inactivation of GLP-1, thereby increasing endogenous levels of GLP-1.

A strong association is evident between gastric emptying time and PPG ($r^2=0.4889$; $p=0.0018$), emphasising the importance of delaying gastric emptying to lower PPG by a GLP-1 receptor agonist.²¹ Shah et al.²² showed that glucagon reduction is another mechanism to reduce PPG, which was confirmed by Ahrén et al.²³ who demonstrated that a reduction in glucagon by DPP-4 inhibition after 4 weeks of therapy correlated to improved glycaemia in subjects with Type 2 diabetes. This supports the role and importance of DPP-4 inhibitors as an intervention to reduce hepatic glucose output and reduce glucagon production. Another factor to target in intervention for PPG is to reduce glucose absorption; e.g., by inhibiting the enzyme α -glucosidase. The latter results in diminished glucose formation, leading to a delayed carbohydrate digestion, reduced rate of glucose absorption, and lower PPG; Hücking et al.²⁵ showed that acarbose, an α -glucosidase inhibitor, reduces PPG by 64% in Type 2 diabetes.^{24,25} Finally, insulin lowers PPG by inhibiting glucagon and hepatic glucose output and enhancing glucose utilisation.

Non-pharmacological Management of High Postprandial Glucose

Ahrén noted that “pharmacological approaches, however, are not sufficient; non-pharmacological tools are also needed for the management of high PPG.” Several nutraceuticals (i.e., food products that are non-specific biological therapies) have been developed and tested.²⁶ These are generally accessible and affordable; however, nutraceuticals have not been studied in as much detail as pharmaceuticals in Type 2 diabetes. Most studies have focused on insulin resistance and few studies on PPG.²⁷ There have been several clinical trials on the use of cinnamon; however, only with regards to HbA1c, fasting blood sugar, and body weight.²⁸ A Cochrane report concluded that there is insufficient evidence to support the use of cinnamon for diabetes.²⁹ A small number of studies on the use of blueberries also exist but no effect on PPG has been demonstrated.³⁰ Ahrén highlighted that the most convincing

effects have been seen with WP and mulberry leaf extracts.

Whey, the liquid remaining after milk has been curdled and strained, contains WP, which may be useful in diabetes. Animal studies have found marked suppression of PPG when WP was used in conjunction with glucose through the mechanisms of increased insulin and GLP-1, and inhibition of DPP-4.³¹ These encouraging results led to a translational study in humans that also showed a reduction in PPG and increase in insulin and GLP-1 when WP was given before a meal, demonstrating the potential of a WP preload to manage PPG in Type 2 diabetes.³² A similar conclusion was reached by Wu et al.³³ who showed that DPP-4 inhibition with vildagliptin augments the beneficial effects (reduction in PPG and increase in GLP-1) of WP. Further clinical studies have been conducted on WP given in different doses and at varying times ahead of a meal, and most have shown a reduction in PPG in Type 2 diabetes.³⁴⁻³⁶ In addition, encouraging long-term effects of WP have been demonstrated, with a sustained reduction in PPG at 12 weeks.³⁷ The exact mechanism of action is not fully understood; however, leucine and isoleucine, but not valine branched-chain amino acids, contained in whey have been shown to reduce PPG.³⁸ Åhrén stated that what is known at present is that “WP, which is rich in branched-chain amino acids and bioactive peptides, stimulates the release of GLP-1 and other gut hormones, inhibits gut DPP-4, delays gastric emptying, stimulates insulin secretion, and reduces appetite, all of which contribute to a reduction in PPG, highlighting its potential benefit for the treatment of Type 2 diabetes.”³⁹ However, limitations exist with traditional WP formulas to regulate PPG. These include the pre-meal timing as most studies have presented WP before a test meal challenge, which is less representative of free-living behaviours (i.e., compliance, forgetfulness, and the burden of planning ahead) and dosing, as evidence to date has primarily used large doses (20–50 g) of WP, entailing a significant caloric load. A novel formulation of WP, in the form of a microgel, has been developed, which allows for the use of highly concentrated WP to be given in small doses. A study that investigated the effects of very-low-dose pre-meal WP microgels in Type 2 diabetes showed a significant reduction in PPG, increased insulin levels, and increased GLP-

1 levels compared to placebo.⁴⁰ These results support the use of WP microgel as a convenient pre-meal shot to improve the postprandial metabolic profile in Type 2 diabetes; however, longer-term studies are needed to understand the full translational metabolic impact of this novel WP microgel formulation.

Mulberry leaf extracts have a long history of use as traditional medicine and one component, 1-deoxynojirimycin (i.e., moranolin), has been shown to competitively inhibit α -glucosidase activity.⁴¹⁻⁴³ A double-blind, randomised, placebo-controlled crossover study showed that mulberry leaf extract (Reducose®; Phynova, Banbury, UK) significantly reduced PPG in healthy subjects compared to placebo.⁴⁴ A further study described a dose-response relationship such that the highest dose (500 mg) reduced PPG by 22%, whereas 250 mg only reduced PPG by 14%. At the lowest dose of 125 mg, no significant difference was observed with mulberry leaf extract compared to placebo.⁴⁵ A meta-analysis of the effects of general mulberry leaf extract on PPG showed a significant reduction by approximately 1 mmol/L in a pooled analysis of 114 subjects, and a sole study on mulberry leaf use in Type 2 diabetes showed a significant reduction in glucose levels.^{46,47}

Åhrén concluded that PPG is an important target to achieve near or absolute normoglycaemia in Type 2 diabetes, with several pharmacological and non-pharmacological interventions for consideration: including insulin, GLP-1 receptor agonists, DPP-4 inhibitors, and α -glucosidase inhibitors; and nutraceuticals, WP, and mulberry leaf extracts, respectively, to reduce PPG. In particular, WP has shown clear benefits on PPG and a novel microgel formulation has the potential to allow for smaller loads to be taken.

Questions and Answers

Are data available regarding the effects of WP on patients with gestational diabetes?

A recent study from China published in August 2021 found a significant reduction in glycaemia in 60 patients with gestational diabetes given 25g WP 30 min prior to a meal.⁴⁸

Is adherence an issue in terms of the need to take WP prior to a meal?

Adherence could be an issue if long-term administration prior to a meal is required. The microgel formulation could be an exciting new solution to avoid the adherence problem, as it can be given much closer in time to the meal with the same effect and a lower amount of whey is required. However, it has not yet been tested in a randomised manner.

Are there any recent studies regarding WP with updated conclusions on the effect on FPG, PPG, as well as HbA1c?

There are no recent data, but it will be important to conduct such studies.

Glycosylated plasma protein after breakfast has the same importance whatever the type of diet. Does it matter if a diet is, for example, higher in protein and lower in carbohydrates? Are there non-pharmacological interventions available for individuals with Type 1 diabetes?

The content of breakfast is different in various countries, but the amount of carbohydrate given at breakfast is similar (30g). With a low glycaemic index or the addition of supplements in the diet, it is important to add these especially at breakfast, particularly in Type 2, and maybe Type 1, diabetes. There are no studies using non-pharmacological treatments in Type 1 diabetes.

Is there potential to use Nestlé's WP microgel in different populations (i.e., pre-diabetes, Type 2, etc.)?

There is the option to use this product in different populations (e.g., gestational diabetes) as it has such a broad mechanism of action.

What impact does exercise have?

There have been no studies to assess this; however, exercise increases insulin sensitivity. Thus, adding a mechanism to reduce PPG following exercise would be extra beneficial.

"All disease begins in the gut" (Hippocrates). Is this true for glucose metabolism and disorders?

Incretins and the gut are important in Type 2 diabetes; however, the β cell (in the pancreas) is the centre stage.

What is the impact of WP on the gut microbiota?

There are ongoing studies to address this, but no conclusions have yet been reached.

How much WP does the microgel formulation contain compared to whey given in a different formulation?

Parallel studies have not been conducted, but whey from the microgel better reaches the site of action and thus has a better effect. The microgel is formulated by Nestlé.

Why do we consider PPG excursions have a direct deleterious effect on cardiovascular risk while the majority of data have demonstrated glycaemic control has an indirect effect on cardiovascular risk?

There is no direct evidence that PPG affects cardiovascular outcome; all evidence is indirect. A controlled randomised trial to demonstrate that postprandial or GV affects cardiovascular outcome would be very difficult to conduct.

To what degree does an elevated PPG level impact the microbiota?

It is unknown whether PPG excursions are deleterious for microvascular circulation or the microvascular system. A challenging study with a difficult design will be required to elucidate this.

Is the PPG limit of 180 mg/dL recommended by the ADA too high?

Yes, as this limit has been set for capillary blood glucose, which is slightly lower than plasma venous blood glucose. A capillary blood glucose of 180 mg/dL corresponds to a plasma venous blood glucose of 200 mg/dL. The IDF recommendation of 160 mg/dL is preferable.

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