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Postprandial and basal hyperglycaemia in type 2 diabetes: Contributions to overall glucose exposure and diabetic complications

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Abstract

Both postprandial and fasting (basal) hyperglycaemia contribute to overall hyperglycaemia (ambient hyperglycaemia) in type 2 diabetes (T2D). Postprandial glucose is the main contributor in fairly well controlled individuals, whereas basal hyperglycaemia becomes the preponderant contributor in poorly controlled patients. A more generally acceptable description of the contribution of postprandial glucose is to simply say that the absolute impact of postprandial glucose to HbA_{1c} remains constant at approximately 1% across the entire HbA_{1c} spectrum of non-insulin-treated patients with T2D. While epidemiological and pathophysiological studies seem to indicate that excessive postprandial glucose excursions play a role in or are predictors of cardiovascular diseases, there is still currently a lack of clinical evidence that correcting post-meal hyperglycaemia can improve clinical outcomes. However, even in the absence of consensus, there are many reasons for thinking that excessive postprandial glucose might be an independent risk factor for diabetic complications as it contributes to both overall glucose exposure and glycaemic variability, especially in those who have HbA_{1c} levels < 7.5–8%. Given that excessive glucose fluctuations from peaks to nadirs activate oxidative stress, it seems reasonable to consider that a key player in the pathogenesis of diabetic complications, according to the latest IDF guidelines, is post-meal glucose, thereby warranting its assessment and treatment when found at abnormally elevated levels. Nevertheless, healthcare professionals should bear in mind that targeting both post-meal and basal plasma glucose, giving equal consideration to both of them, is probably the best strategy for achieving optimal glycaemic control and thus preventing or reducing the risk of diabetic complications.

Key words: Postprandial glucose; Basal glucose; Overall glucose exposure; Type 2 diabetes; Diabetic complications

1. Glucose disorders in diabetes and its complications

From a glucocentric point of view, three glycaemic disorders can be identified at the heart of the risk for cardiovascular diseases in people with diabetes: basal hyperglycaemia; postprandial glucose excursions; and glycaemic variability [1]. Postprandial glucose (PPG) excursions play a pivotal role as they contribute, first, to overall glucose exposure in combination with basal hyperglycaemia and, second and for obvious reasons, to glycaemic variability. Although, for many years, glycated haemoglobin (HbA_{1c}) has been used as the main marker for assessing overall glucose exposure (ambient hyperglycaemia) in diabetes [2], there remains the fact that measurement of this parameter does not provide any data for investigating the contributions of the three above-mentioned components of the dysglycaemia seen in people with diabetes.

More specifically and from a clinical point of view, it is important to assess the potential contribution and roles of fasting (basal) and post-meal hyperglycaemia in the decision-making process for therapeutic choices in type 2 diabetes (T2D). This assertion can be illustrated by considering four clinical situations (Fig. 1), each of which corresponds to patients in whom mean glucose concentrations (ambient hyperglycaemia) and glycaemic variability are at different degrees of impairment within the context of HbA_{1c} levels at 7% and 8% for ambient hyperglycaemia and small or large glucose oscillations from peaks (PPG concentrations at the time point of maximum glucose excursions) to nadirs (the lowest glucose values during either interprandial or fasting periods). Intuitively, healthcare professionals believe that the best metabolic status is found in patients who have low mean glucose concentrations (HbA_{1c} at approximately ≤ 7%) concomitantly with minimal glucose variability. In contrast, patients with HbA_{1c} at 8% have an undoubted increased risk for vascular diseases, as the central role of ambient hyperglycaemia in the development or progression of long-term diabetic complications has been clearly established [3] and confirmed [4] in T2D. The intermediate situation corresponds to a patient who

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has a total glucose exposure that is relatively low (HbA_{1c} at 7%), but with glucose concentrations that fluctuate excessively. Clearly, such a patient is at increased risk of hypoglycaemia and, therefore, the selected antidiabetic treatment should be aimed at smoothing out glucose variability [5].

2. Role of PPG excursions and basal glucose in overall hyperglycaemia in T2D

In 2003, our seminal report published in *Diabetes Care* initiated this recurring debate [6]. Despite the ever-increasing body of evidence for the contribution of PPG to overall hyperglycaemia [7–9], this glycaemic disorder has remained for many years a second- or third-line target in the treatment of overall hyperglycaemia compared with "basal" hyperglycaemia [10,11]. However, the past few years have witnessed the development of a new class of short-acting glucagon-like peptide-1 (GLP-1) receptor agonists such as lixisenatide, which predominantly targets prandial glucose excursions [12]. These new agents have proven their efficacy in both post-meal glucose excursions and overall glycaemic control [13], and even in patients being treated with an ongoing basal insulin regimen [14].

As a consequence, there is increasing evidence to support giving more due consideration to postprandial hyperglycaemia and recommending its reduction as a relevant clinical goal. As mentioned above, using a four-point glucose profile [6], it has been demonstrated that the relative contribution of PPG to overall hyperglycaemia is particularly marked in well or satisfactorily controlled T2D patients ($HbA_{1c} < 7.3\%$). When HbA_{1c} is between 7.3% and 8.4%, the relative contributions of postprandial and basal hyperglycaemia to overall glucose exposure become approximately equivalent whereas, beyond 8.4%, basal hyperglycaemia becomes predominant (Fig. 2).

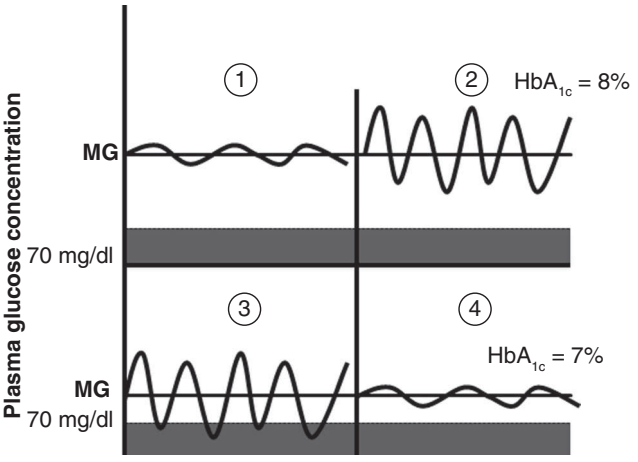

Fig. 1. An illustration of four clinical situations of four theoretical patients with different levels of HbA_{1c} (8% in patients 1 and 2; 7% in patients 3 and 4), and with small (patients 1 and 4) or large (patients 2 and 3) oscillations around the mean glucose (MG) value. Intuitively, patient 4 would appear to have the best metabolic status, with an HbA_{1c} of 7% and little glycaemic variability.

This observation is simply due to the fact that the absolute contribution of postprandial hyperglycaemia across the increasing HbA_{1c} spectrum remains stable at approximately 1% of HbA_{1c} (as a percentage point) for levels > 7% (Fig. 3) [15]. Thus, any increase in glucose exposure beyond this threshold (HbA_{1c} at 7%) is due to a linear increase in basal hyperglycaemia, thereby representing its ever-increasing relative contribution; this becomes especially evident at an HbA_{1c} cut-off value of 8–8.5% or over [16].

These results were obtained by analyzing the 24-h glycaemic profiles of 140 non-insulin-treated patients with T2D, who were investigated by using both continuous glucose monitoring [15,16] and glucose mathematical calculations and principles. At an individual level, overall glucose exposure can be estimated by calculating the total area under curve of the 24-h glycaemic profile above zero (AUC_{total}). Postprandial increments (AUC_{pp}) can be measured by calculating the area above the preprandial value over a 4-h period after the start of each meal. Accordingly, the absolute impact of the PPG

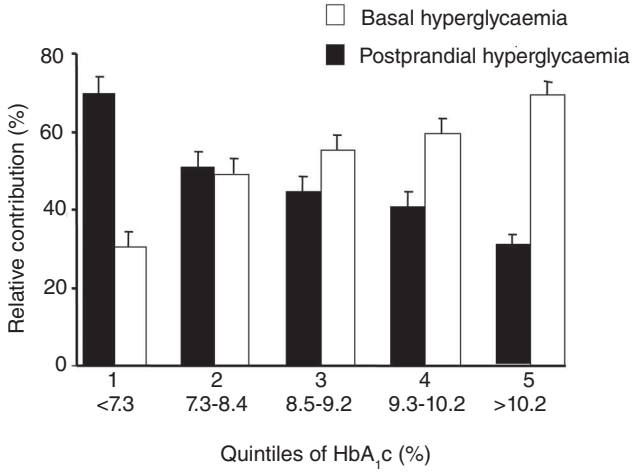

Fig. 2. Bar graph of the relative contributions of postprandial and fasting hyperglycaemia (%) to overall diurnal hyperglycaemia across quintiles of HbA_{1c} levels [6].

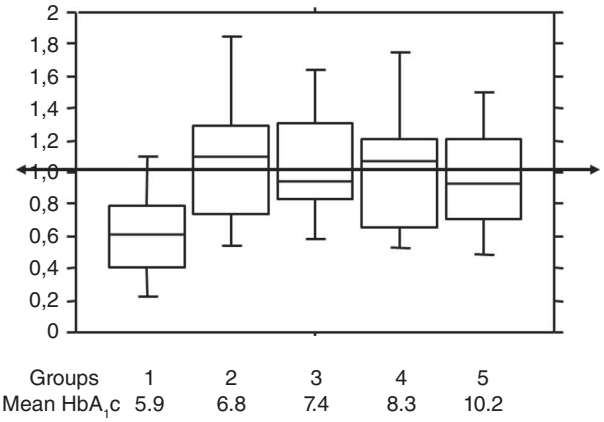

Fig. 3. Graph showing the absolute impact of postprandial glucose increments on HbA_{1c} (percentage points, medians with interquartile range; 10th and 90th percentiles) with worsening diabetes in non-insulin-treated patients with type 2 diabetes [15].