

Three key indices in clinical practice to better comprehend the postprandial and basal glucose contributions in type 2 diabetes

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It is well acknowledged that the excess overall exposure to glucose in diabetes is the arithmetic sum of postprandial and basal glucose increments above normal levels [1]. In 2003, our pivotal publication in *Diabetes Care* initiated the debate on the respective contribution of postprandial glucose excursions and basal glucose increments to the overall hyperglycemia in persons with type 2 diabetes [2]. Even though at that time the design of the study was limited to the analysis of discontinuous diurnal glycemic profiles, we observed that the postprandial hyperglycemia is the main contributor to the overall hyperglycemia in fairly well controlled persons (HbA1c < 7.3%, 56 mmol/mol) while its relative contribution progressively decreased with worsening diabetes becoming less than that of basal glucose in those poorly controlled with a HbA1c level > 8.5% (69 mmol/mol). Subsequently, the

use of the continuous glucose monitoring (CGM) enabled to define more accurately the HbA1c threshold that separates the different stages of the disease according to whether postprandial or basal hyperglycemia predominates [3,4]. As schematically illustrated in the figure adapted from our previous publications [3,4], the main stages of glycemic disorders are: Stage 1 (prediabetes) limited to the dawn phenomenon when HbA1c levels range from 5.7 to 6.4% (39-46 mmol/mol); Stage 2 (overt diabetes) with an additional excess postprandial glucose elevations especially after breakfast in those with HbA1c levels between 6.5 and 6.9% (48-52 mmol/mol) and Stage 3 with progressive increases in basal hyperglycemia as soon as HbA1c levels are equal to or exceed 7% (53 mmol/mol). When the HbA1c exceeds 7% (53mmol/mol) the absolute contribution of postprandial excursions (AUC_{pp}) remains relatively constant, approximating a percentage point of 1% (11mmol/mol), whereas the absolute contribution of the basal hyperglycemia (AUC_{basal}) continues to increase linearly [2]. The postprandial excursions and basal glucose increments contribute equally to the overall hyperglycemia when HbA1c levels remain between 7 and 8% (53 and 64 mmol/mol). However, when the HbA1c increases beyond 8% (64 mmol/mol) the basal glucose increments become the major contributor (figure).

In this issue of Diabetes Technology and Therapeutics, the article by Uemura et al [5] confirms our previous findings and conclusions. By substituting the TIR (%Time In Range between 70 and 180 mg/dL, i.e., 3.9 and 10.0 mmol/L) for the HbA1c and by applying the ROC curve methodology to the TIR they found that a TIR value of ~ 66% best separates those persons in whom postprandial excursions (AUC_{pp}) or basal glucose increments (AUC_{basal}) are major contributors [5]. This value corresponds to an HbA1c level of 7% (53 mmol/mol) according to the relationship established when the HbA1c is plotted against the TIR [6,7]. In addition, whereas the AUC_{pp} increases progressively with increasingly good control ($TIR \geq 66\%$) it reaches a plateau when the TIR decreases below ~ 66% (HbA1c = 7%, 53mmol/mol).

When considering these complementary findings there are three key indices that should be borne in mind and which could be useful in clinical practice.

Firstly, 7% (53 mmol/mol) for the HbA1c (i.e. ~ 66% for the TIR) can be regarded as the cut-off value which differentiates between the two main contributors of the excess hyperglycemia in type 2 diabetes. This threshold can therefore be helpful to choose the most relevant pharmacological therapy necessary and thus represent one of the steps to implement the precision medicine in the management of type 2 diabetes.

Secondly, 1% of HbA1c (11 mmol/mol) is the absolute impact of postprandial glucose excursions across the increasing HbA1c spectrum beyond 7% (53 mmol/mol) and this absolute contribution

remains stable regardless of the HbA1c level. Consequently, in a person with a HbA1c level > 7% (53 mmol/mol), even a clinically significant reduction in postprandial excursions will only have a relatively small impact on the overall glycemic control necessitating concomitant therapy to reduce the basal hyperglycemia to achieve a near normal glucose homeostasis.

The need to limit postprandial glucose elevations cannot be ignored especially when individuals consume up to 3 meals per day, which means up to 12 hours in the postprandial state [8,9]. Therefore, 50% is the third index number, which corresponds to the percentage of time during a full day when individuals are in postmeal states [8]. It is worth noting that in persons with type 2 diabetes the greatest postprandial glucose excursions usually occur 60-to-120 minutes after breakfast [3] when the glucose tolerance is worse in the early morning [10] and when the spontaneous prebreakfast glucose rise at the end of the nocturnal period has a remnant impact on the post-breakfast glucose increments [11]. However, there is still an endless debate to know whether excessive postprandial excursions are glucose values above 180 mg/dL (10.0 mmol/L) as recommended by the American Diabetes Association [12] or 160 mg/dL (8.9 mmol/L) recommended by the International Diabetes Federation [13]).

At the end of this commentary, we should bear in mind that the 3 aforementioned key indices/metrics are aimed at promoting a more pathophysiological approach for controlling the 24-h glycemic profiles and thereby preventing the development and progression of diabetes-related complications [14].

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Legend of the figure

Illustration of the continuum in the deterioration of the different components of glycaemic disorders (the dawn phenomenon, postprandial glucose excursions and basal glucose increments) with diabetes worsening and throughout the natural history of type 2 diabetes

