Below which threshold of glycemic variability is there a minimal risk of hypoglycemia in people with type 2 diabetes?

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Managing glycemic control in persons with diabetes consists of achieving a balance aimed at reducing the risks due to chronic –ambient- hyperglycemia, postprandial glucose excursions, glycemic variability and hypoglycemia referred to as the “ominous quartet”. These components of dysglycemia are interconnected to a various degree with a higher incidence of hypoglycemia when attempting to improve ambient hyperglycemia [1-3]. In contrast, it has also been demonstrated that the smaller the within-day glucose variability the lower the risk for hypoglycemic episodes [4]. Consequently, attempting to reduce the chronic glucose exposure should be associated with a concomitant diminution in daily glucose fluctuations.

On the basis of our own data [5] the international consensus conference on the use of continuous glucose monitoring [6] has adopted a coefficient of variation for glucose (%CV = SD/24-h mean glucose) of 36% as a suitable cut-off value to distinguish between stable and unstable glycemia in diabetes. Stable diabetes corresponds to less frequent and severe hypoglycemia, which does not necessarily mean that hypoglycemic episodes would be eradicated or the time below range (TBR Level 2) <54 mg/dL (<3 mmol/L) would be reduced to below 1% [7].

In the present issue of Diabetes Technology and Therapeutics, Uemura et al [8] have observed that maintaining a TBR below 1% requires maintaining an average glucose level above 7.19 mmol/L and a %CV less than 30.3%. A 24-h mean glucose concentration of 7.19 mmol/L (129 mg/dL) corresponds to an estimated HbA1c levels of 6.4% (46.4 mmol/mol) [9], and therefore it can be considered that a %CV < 30.3% is a relevant target for reducing the risk of hypoglycemia to a low level. However, whether this glucose variability target is sufficiently low to achieve a minimal risk of hypoglycemia, remains to be answered. Insights into this issue can be gained from studies in individuals without diabetes [10,11] and particularly in those where the %CV has been reported to be within the range of 12-18% [12,13]. A study conducted by Shah et al [13] in healthy people with a HbA1c < 5.7% (< 38.7 mmol/mol) wearing a continuous glucose monitoring (Dexcom G6 system) for approximately 10 days on an ambulatory basis, has revealed that for an average 24-h glucose of 99 ± 7 mg/dL (5.49 ± 0.39 mmol/L), the within-individual coefficient of variation for glucose is 17 ± 3% (mean ± SD) and that the median TBR < 3 mmol/L is equal to 0% (quartiles: 0.0% to 0.2%). Should the shape of glucose distribution be assumed as being Gaussian, 99.9% of the %CV values would be within the mean ± 3.31 SD and the %CV for glucose would be always < 27% in non-diabetic healthy individuals. This does not mean that people with a %CV < 27% are not subject to hypoglycemic events because, even in people with normal tolerance to glucose, it has been demonstrated that 28% of them persisted to experience hypoglycemic episodes [13].

Reverting to type 2 diabetes treated with either oral hypoglycemic agents alone or in combination with insulin and when using a cross tabulation with the 48-h mean glucose concentration and the SD for glucose on the x and y axis, respectively, and with the number of hypoglycemic events < 56 mg/dL (3.11 mmol/L) on the vertical axis, we observed that the risk of developing hypoglycemia was completely absent when the mean glucose concentration and the SD for glucose were concomitantly > 7.8 mmol/L and < 2.2 mmol/L, i.e. when the %CV was < 28% [14]. Such findings are in agreement not only with the data published in normoglycemic persons [13] but also with those reported by Rodbard for people with type 1 and type 2 diabetes [15]. After normalizing the usual rightward skewed distribution of glucose values, this author found a highly positive significant correlation (r = 0.49) between the %CV and the risk for hypoglycemia assessed from TBR < 50 mg/dL (2.8 mmol/L). In addition, by extrapolating the regression line to its intercept with the TBR value of 0%, it appears that the corresponding %CV is approximately of 27% [15], a value in agreement with that computed from the 99.9th percentile of %CV in healthy non-diabetic individuals [13].

Bringing all these findings together [13-15] and to include the more recent findings by Uemura et al [8], it seems highly likely that in people with type 2 diabetes treated with either insulin and/or non-insulin glucose-lowering agents the risk for hypoglycemia is minimal when the %CV is strictly maintained below 27%, remains relatively low when the %CV is between 27 and 31%, whereas the risk increases steadily with a %CV above 31% .

An additional question is which sector of people with type 2 diabetes is at greatest risk of hypoglycemia. From histograms depicting the relative frequency of %CV for glucose it appears that the proportion of subjects with %CV > 27% remains small (< 15%) in those who are treated with non-insulinotropic oral hypoglycemic agents such as metformin or DPP-4 inhibitors [5]. However, the proportion of subjects with %CV > 27% increases to above 30 % in those treated with sulfonylureas and 50% when receiving insulin therapy, respectively [5]. This data is in agreement with the findings

by Uemura et al of a more prolonged TBR in people with type 2 diabetes treated with sulfonylureas or insulin [8].

At the end of this commentary one can therefore conclude that in type 2 diabetes it remains difficult to delineate the boundaries of short-term glycemic variability between those who are at low, medium and high risk for hypoglycemia even though there is no doubt that this risk depends on both glycemic variability and the mean ambient blood glucose level [16]. However, a %CV of ≤ 27% could be a reasonable recommendation to minimize the risk of hypoglycemic episodes < 54 mg/dL (3 mmol/L) in many situations. An even lower threshold could be more appropriate when the mean glucose concentrations are below 120 mg/dL (6.7 mmol/L) [16].

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