COMMENTARY

Measures of Risk and Glucose Variability in Adults Versus Youths

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THE ARTICLE BY PATTON ET AL.¹ PUBLISHED in this issue of *Diabetes Technology & Therapeutics* reports an array of correlations between various metrics of glucose variability (GV), derived from 1 month of self-monitoring of blood glucose (SMBG) data, with the frequency of hypo- and hyperglycemic events in a subsequent month of SMBG records. The data were derived from the clinical patient records of 3,453 individuals, 436 of whom met the study inclusion criteria (e.g., ages between 0 and 18 years old and a minimum of 14 days of SMBG in each month with three or more SMBG values per day). The purpose of the study was to assess whether the Average Daily Risk Range (ADRR), introduced in 2006 as a risk-based metric of GV, is a valid predictor of hypo- and hyperglycemia in youths with type 1 diabetes. The other GV metrics used for this prediction included SD and coefficient of variation of blood glucose (BG), Low Blood Glucose Index (LBGI), High Blood Glucose Index (HBGI), the percentage of glucose values >70 and <180 mg/dL, the percentage of high glucose values >180 mg/dL and >400 mg/dL, and the percentage of low glucose values <70 mg/dL and <40 mg/dL in Month 1. Patton et al.¹ concluded that “In a large pediatric sample, the ADRR was not the strongest predictor of future glycemic excursion. The percentages of current hyper- and hypoglycemic episodes appear to be stronger predictors.”

This conclusion somewhat contradicts the original ADRR findings in adults² and the conclusions of a recent review of this metric, which stated “Glycemic variability is masked by HbA1c [hemoglobin A1c], but counseling patients based on their ADRR scores may help them to achieve more normalized blood glucose levels and improve their quality of life and health outcomes.”³ Moreover, new reports in type 2 diabetes^{4,5} that investigated a large sample of 1,699 patients undergoing insulin treatment concluded that “During glucose-lowering therapy in T2DM [type 2 diabetes mellitus], HBGI and LBGI offer insights into hyperglycemia and trends toward hypoglycemia, respectively; ADRR may be the optimal GV measure responsive to hypo- and hyperglycemic treatment effects.”⁵

It may be therefore useful to speculate why the same metric has different predictive ability in different age groups and whether age-specific variants of the ADRR and of the other two risk-based metrics—the LBGI and the HBGI—are

warranted as suggested: “New ADRR risk guidelines are needed for pediatric patients.”⁶ In order to make an informed speculation, we would need to recall the basics of the risk analysis of BG data,^{7–9} which unifies the LBGI, the HBGI, and the ADRR into a single mathematical framework based on a logarithmic function symmetrizing the BG measurement scale. Notably, this transformation has not changed its analytical formula since its introduction in 1997⁷ and is still in use in applications ranging from risk analysis in type 1 diabetes^{1–3,6–10} and assessment of medication effects in type 2 diabetes^{4,5} to defining risk traces in continuous glucose monitoring data^{11,12} and the design of safety algorithms for closed-loop control systems in artificial pancreas studies.^{13,14}

The roots of the BG scale transformation and its corresponding BG risk function can be traced to the clinical notion of “target range.” Because patients with diabetes face the lifelong optimization problem of reducing average glycemic levels (e.g., HbA1c) and postprandial hyperglycemia while simultaneously avoiding hypoglycemia, a typical clinical advice is to keep BG levels into a target range (e.g., 70–180 mg/dL). Consistent with this advice, measures of glycemic variability should place progressively increasing weights (or penalties) on BG readings exceeding the limits of the desired target range. For example, in a GV calculation, an SMBG reading of 45 mg/dL should weight more heavily in terms of risk associated with hypoglycemia than an SMBG reading of 65 mg/dL. Such an approach corresponds to the notion that the glycemic risk increases progressively as BG levels move farther away from their zero-risk target value. Calculating percentages of hypo- or hyperglycemic readings does not meet this requirement: in a percentage calculation readings of 45 mg/dL and 65 mg/dL are weighted equally.

Most traditional metrics of GV—SD, coefficient of variation, the M-value (introduced in 1965),¹⁵ the mean amplitude of glucose excursions (introduced in 1970),¹⁶ or the Glycemic Lability Index¹⁷—do not use weighting of BG observations as well. In contrast, the LBGI, HBGI, and ADRR are based on the transformed BG scale and on its corresponding BG risk function, placing increasing weights on progressively lower and progressively higher values. As presented in Figure 1A, the increase of the BG risk function is steeper when BG values advance into hypoglycemia.

FIG. 1. (A) The blood glucose (BG) risk function introduced in 1997, which assumes a target range of 70–180 mg/dL. The left branch represents risk for hypoglycemia, increasing steeply when BG levels move downward from 112.5 mg/dL; the right branch represents risk for hyperglycemia, increasing gradually when BG levels move upward from 112.5 mg/dL. (B) Variants of the BG risk function using different zero-risk target values and target ranges as presented in Table 1. Each one of these variants, as well as any other analytically derived intermediate variants, can serve as a base for redefining the Low BG Index, the High BG Index, and the Average Daily Risk Range for a specific population.

TABLE 1. CORRESPONDENCE AMONG TARGET VALUES, PARAMETERS (α , β , AND γ) OF THE BLOOD GLUCOSE SCALE TRANSFORMATION, AND BLOOD GLUCOSE TARGET RANGES

<i>Zero-risk BG target</i>	α	β	γ	<i>Target range</i>
90	0.384	1.782	12.269	57–147 mg/dL
100	0.713	2.971	4.032	62–163 mg/dL
112.5	1.084	5.381	1.509	70–180 mg/dL ^a
120	1.293	7.573	0.919	75–192 mg/dL
160	2.298	41.820	0.108	100–240 mg/dL
200	3.244	223.357	0.017	130–288 mg/dL

^aRepresents the zero-risk blood glucose (BG) target, parameters, and target range of the original BG scale transformation.

Back in 1997, the formula of the scale transformation was based on the assumption that the treatment target range was 70–180 mg/dL, not on a particular dataset. This assumption led to two equations that, when solved numerically, fixed the parameters of the BG scale transformation at their past (and present) values⁷ and predetermined the zero-risk center of the BG scale at 112.5 mg/dL—a clinically safe euglycemic target value (Fig. 1A).

Since then, the target range, the zero-risk target value, and therefore the definitions of the LBGI, HBGI, and ADRR worked well to assess risks for hypo- and hyperglycemia in many studies involving adults with type 1 and type 2 diabetes. For children, these metrics continue to perform in the hyperglycemic range,^{1,6} and the LBGI works as designed in the hypoglycemic range as well (Table 1 in Patton et al.¹). However, according to this latest report, the predictive value of the ADRR may be weaker in the pediatric population.¹ This may be due to artifacts in the study, such as the very low frequency of extreme low BG events (<40 mg/dL), which was 0.3% according to the text or 0.03% according to Table 2 in Patton et al.¹ Statistically, it is natural to expect that low frequency of extreme hypoglycemia would result in near-zero correlation for metrics tuned to detect extreme hypoglycemia such as the ADRR; it is also normal that metrics taking into account all low BG values (e.g., the LBGI or the percentage of readings below a certain threshold) would perform better, as evidenced by Table 1 in Patton et al.¹

Assuming, however, that the effect is real and is due to the specifics of the studied population, a correction of the ADRR may be in order for pediatric patients, and the metric may indeed require “new guidelines.”⁶ Figure 1B presents a possible solution to this problem, derived from the basic definition of the BG scale transformation function. Specifically, adjusting the clinical zero-risk BG target value (or equivalently, the target range) for a specific subpopulation will result in different shapes of the BG risk function and thereby in different weighting of the BG scale. All risk-based metrics—LBGI, HBGI, and ADRR—will change their values and their sensitivities to hypo- and hyperglycemic events. Table 1 presents the target values, the recomputed parameters (α , β , and γ) of the BG scale transformation,⁷ and the target ranges corresponding to the risk curves in Figure 1B.

In conclusion, new pediatric-specific guidelines can be derived for all risk-based metrics of GV—LBGI, HBGI, and ADRR—using the computational flexibility embedded

in their original design. These guidelines could include adjustment of the risk thresholds for these metrics (currently 20 and 40 for the ADRR) or could be based on redefining the notion of target range or zero-risk value for any specific population. The latter will result in redefined BG weightings, potentially reflecting better the clinical understanding of the risks associated with deviations into hypo- or hyperglycemia that are specific to this population. The BG risk function can be also manipulated directly as it was done in a previous study defining fetal versus maternal risks in pregnancy.¹⁸ This previous study reflected the clinical understanding of the distinct risks a BG value carries for the fetus and for the mother, implemented this understanding in a new risk function, and concluded that “This new risk assignment better distinguishes the stages of fetal risk than the original method and therefore may be useful in future clinical trials and applications to predict risk for adverse outcomes in pregnancies complicated by diabetes.”¹⁸ Thus, modification of the LBGI, HBGI, and ADRR may be indeed due for pediatric patients to reflect better the specific of GV in adults versus youth and can be done seamlessly using the mathematical fundamentals behind these metrics.

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