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Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes

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1 | INTRODUCTION

It is well established that hypoglycemia is a core outcome to be measured and recorded in diabetes management whether for individual patient care, audit of therapies and clinical services, or in research and clinical trials. Although it is recognized that no single glucose level can define hypoglycemia in an individual, it is important to have accepted definitions to allow valid comparisons between models of care and therapies and the prospective evaluation of outcomes over time. Inconsistencies in definitions and changes in definitions have made such comparisons difficult.

2 | COMMENTARY

The American Diabetes Association (ADA) has chosen a nonnumerical definition of hypoglycemia because thresholds for symptoms and cognitive dysfunction vary between individuals and are influenced by factors such as age¹, previous hypoglycemia exposure,² and glycemic control.^{3,4} Hypoglycemic events have been defined, therefore, to include all episodes of a plasma glucose concentration low enough to expose the individual to potential harm.⁵ Despite this, the importance and potential benefits of establishing a specific and meaningful definition of hypoglycemia risk have been recognized.

Recently, in an article published simultaneously by the ADA and the European Association for the Study of Diabetes (EASD), the International Hypoglycemia Study Group (IHSG) suggested that it would be useful for the diabetes community to adopt a common approach to address the issue of hypoglycemic risk. The IHSG suggested 3 levels: these included an “alert” value of less than 3.9 mmol/L (70 mg/dL), a biochemically defined glucose level that may be considered clinically important or serious of <3.0 mmol/L (54 mg/dL) and a clinically defined level of severe hypoglycemia as previously defined by the ADA (severe cognitive impairment requiring external assistance for recovery).⁶ It was suggested that

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acceptance of this approach would allow the evaluation of a therapy over time and also comparisons between therapies in clinical trials and cohort studies and facilitate meta-analyses of different studies. Recently, in addition to the IHSG position statement, the advent of more widespread use of continuous glucose monitoring (CGM) and other diabetes technologies has led to other consensus groups addressing the need to have a common approach to the definition of glycemic metrics including hypoglycemia.^{7–10}

In an attempt to standardize definitions in pediatric diabetes care and research, as well as to align with recent proposals for a common approach to be adopted, the latest ISPAD guidelines have proposed the following definitions and levels of hypoglycemia risk. Although there are data to suggest different glucose levels at which counter regulation may be initiated in the young,¹ it was considered that these were small in comparison to other factors that may influence these thresholds. It was also considered to be of benefit to have pediatric and adult measures aligned.

The following definitions were suggested:

1. Clinical hypoglycemia alert: A glucose alert value of ≤ 3.9 mmol/L (70 mg/dL) is an alert value that requires attention to prevent hypoglycemia. The alert can be used as the threshold value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further.
2. Clinically important or serious hypoglycemia: A glucose value of < 3.0 mmol/L (54 mg/dL) indicates serious, clinically important hypoglycemia. Although there are no specific pediatric studies which directly support this numerical cut-off, these low levels are more likely to cause defective glucose counter regulation¹¹ and impaired awareness of hypoglycemia with increased risk of severe hypoglycemia. This level has also been associated with neuroglycopenia and cognitive dysfunction.^{12,13} This level should be recorded in routine clinical care and reported in audits and clinical trials of interventions directed towards reducing hypoglycemia (as recommended by the IHSG).⁶
3. Severe hypoglycemia: It is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. This aligns with the definition of severe hypoglycemia in adults in accordance with the ADA guidelines.⁵ This definition has been to a certain extent problematic in young children because at this age they all may require assistance to correct even mild hypoglycemia. To determine whether hypoglycemia is severe by this definition in young children will require an assessment and a judgment by the caregiver and clinician as to the presence or not of hypoglycemia-induced cognitive dysfunction. Despite the difficulty of definition at this age, it was considered important to record such events. This will also enable complete recording of events vs underestimation of severe hypoglycemia frequency in children if defined by coma or convulsions only. This expanded definition has been used in the past in children in previous observational studies on severe hypoglycemia. A subgroup of severe

hypoglycemia is severe hypoglycemic coma which is described as a severe hypoglycemic event resulting in coma or convulsion requiring parenteral therapy: such events have reduced in frequency over the last decade in some major cohorts.^{17,18} The ISPAD guidelines group considered that it was important to continue to record these events as a subgroup because they are unequivocal in definition and significant in outcome.

As the choices of therapies in diabetes care multiply and the recognition of the importance of hypoglycemia and hypoglycemia fear increases, it is essential to standardize the approach to measuring and recording hypoglycemia risk. These developments are occurring at a time when the capacity to record data to monitor outcomes has increased significantly. Standardizing what is measured is not only important to assess the effectiveness and efficacy of therapies but will also inform both the economic assessment that is critical for funders and enable informed choices to be made by patients and clinicians.

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