Standardizing Clinically Meaningful Outcome Measures Beyond HbA_{1c} for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange

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OBJECTIVE

To identify and define clinically meaningful type 1 diabetes outcomes beyond hemoglobin A_{1c} (HbA_{1c}) based upon a review of the evidence, consensus from clinical experts, and input from researchers, people with type 1 diabetes, and industry. Priority outcomes include hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis (DKA), and patient-reported outcomes (PROs). While priority outcomes for type 1 and type 2 diabetes may overlap, type 1 diabetes was the focus of this work.

RESEARCH AND METHODS

A Steering Committee—comprising representatives from the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange—was the decision-making body for the Type 1 Diabetes Outcomes Program. Their work was informed by input from researchers, industry, and people with diabetes through Advisory Committees representing each stakeholder group. Stakeholder surveys were used to identify priority outcomes. The outcomes prioritized in the surveys were hypoglycemia, hyperglycemia, time in range, DKA, and PROs. To develop consensus on the definitions of these outcomes, the Steering Committee relied on published evidence, their clinical expertise, and feedback from the Advisory Committees.

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RESULTS

The Steering Committee developed definitions for hypoglycemia, hyperglycemia, time in range, and DKA in type 1 diabetes. The definitions reflect their assessment of the outcome's short- and long-term clinical impact on people with type 1 diabetes. Knowledge gaps to be addressed by future research were identified. The Steering Committee discussed PROs and concluded that further type 1 diabetes–specific development is needed.

CONCLUSIONS

The Steering Committee recommends use of the defined clinically meaningful outcomes beyond HbA_{1c} in the research, development, and evaluation of type 1 diabetes therapies.

Type 1 diabetes is a life-threatening, autoimmune disease that strikes children and adults and can be fatal. People with type 1 diabetes have to test their blood glucose multiple times each day and dose insulin via injections or an infusion pump 24 h a day every day. Too much insulin can result in hypoglycemia, seizures, coma, or death. Hyperglycemia over time leads to kidney, heart, nerve, and eye damage. Even with diligent monitoring, the majority of people with type 1 diabetes do not achieve recommended target glucose levels. In the U.S., approximately one in five children and one in three adults meet hemoglobin A_{1c} (HbA_{1c}) targets and the average patient spends 7 h a day hyperglycemic and over 90 min hypoglycemic (1–3). The disease burden of type 1 diabetes can negatively impact quality of life, including finances and careers. In addition, the stress on and amount of time required of caregivers, including parents and children caring for aging parents living with type 1 diabetes, also burdens the entire family. There remains significant room for further improvement in the therapies and technologies designed to treat and assist in the management of this disease and prevent its life-threatening complications.

HbA_{1c} is a well-accepted surrogate outcome measure for evaluating the efficacy of diabetes therapies and technologies in clinical practice as well as in research (4–6). For the purposes of this article, the Steering Committee is using the Centers for Disease Control and Prevention's definition of population health outcomes, defined as a population's dynamic state of physical, mental, and social well-being (7). While HbA_{1c} is used as a primary outcome to assess glycemic control and as a surrogate for risk of developing complications, it has limitations. As a measure of mean blood glucose over 2 or 3 months, HbA_{1c} does not capture short-term variations in blood glucose or exposure to hypoglycemia and hyperglycemia in individuals with type 1 diabetes; HbA_{1c} also does not capture the impact of blood glucose variations on individuals' quality of life. Recent advances in type 1 diabetes technologies have made it feasible to assess the efficacy of therapies and technologies using a set of outcomes beyond HbA_{1c} and to expand definitions of outcomes such as hypoglycemia. While definitions for hypoglycemia in clinical care exist, they have not been standardized among organizations and there is inconsistency in the definitions used in different research studies. The lack of standard definitions impedes and can confuse their use in clinical practice, impedes development processes for new therapies, makes comparison of studies in the literature challenging, and may lead to regulatory and reimbursement decisions that fail to meet the needs of people with diabetes.

To address this vital issue, the type 1 diabetes–stakeholder community launched the Type 1 Diabetes Outcomes Program to develop consensus definitions for a set of priority outcomes for type 1 diabetes. A Steering Committee—comprising representatives from the American Association of Clinical Endocrinologists (AACE), the American Association of Diabetes Educators (AADE), the American Diabetes Association (ADA), the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society (PES), and the T1D Exchange—was the decision-making body for the Type 1 Diabetes Outcomes Program. The work of the Steering Committee was informed by diabetes researchers, industry, and people with diabetes through Advisory Committees representing each stakeholder group (Supplementary Data). The Steering Committee met for distinct in-person meetings in May and August 2016 to review the existing evidence and discuss and come to consensus on definitions for each priority outcome. Teleconferences and surveys of Advisory Committee members also informed discussions of outcome definitions. JDRF paid the expenses for this group, including teleconferences, travel expenses, and consulting services to facilitate group discussion, funded in part by a grant from The Leona M. and Harry B. Helmsley Charitable Trust. A draft consensus statement was posted on JDRF's website for 30 days in March 2017 to allow for public comments.

The outcomes prioritized under the program include hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis (DKA), and patient-reported outcomes (PROs). The Steering Committee, with input from the Advisory Committees, came to consensus on standardized definitions for each outcome based on published evidence and their expert opinion (or, in the case of PROs, a consensus that further type 1 diabetes–specific PRO development was needed). The focus for this program was type 1 diabetes, although the literature reviewed included data from people without diabetes and with type 2 diabetes to support the consensus statement. A parallel article published in this issue of *Diabetes Care* focuses more broadly on diabetes, and it is notable that the definitions reached are the same for both groups (8).

The immediate goal of the Type 1 Diabetes Outcomes Program was to identify and provide standardized definitions for an expanded set of clinical outcomes for research aimed at the development and evaluation of new diabetes therapies and technologies. It is not our expectation for any of the outcomes defined in this document to replace HbA_{1c}, as it remains an important outcome measure, but rather that they supplement its utility and allow for the capture of a more comprehensive understanding of how interventions might influence people with diabetes. The goal of the program is to ensure that defined outcomes are included as primary and secondary end points in type 1 diabetes research, development, and evaluation for future therapies.

For each outcome, the Steering Committee was asked to ensure that the consensus definition met the following criteria:

- Clinically meaningful
- Applicable to the nonpregnant population with type 1 diabetes
- Measurable using existing tools
- Applicable regardless of time of day (e.g., pre- and postprandial, day and night)

A summary of the consensus definitions is shown in Table 1, and a discussion of each outcome is provided in the following sections.

HYPOGLYCEMIA

Hypoglycemia is a significant—and potentially fatal—complication of type 1 diabetes management and has been found to be a barrier to achieving glycemic goals (9). Repeated exposure to severe hypoglycemic events has been associated with an increased risk of cardiovascular events and all-cause mortality in people with type 1 or type 2 diabetes (10,11). Hypoglycemia can also be fatal, and severe hypoglycemic events have been associated with increased mortality (12–14). In addition to the physical aspects of hypoglycemia, it can also have negative consequences on emotional status and quality of life.

While there is some variability in how and when individuals manifest symptoms of hypoglycemia, beginning at blood glucose levels <70 mg/dL (3.9 mmol/L) (which is at the low end of the typical postabsorptive plasma glucose range), the body begins to increase its secretion of counterregulatory hormones including glucagon, epinephrine, cortisol, and growth hormone. The release of these hormones can cause moderate autonomic effects, including but not limited to shaking, palpitations, sweating, and hunger (15). Individuals without diabetes do not typically experience dangerously low blood glucose levels because of counterregulatory hormonal regulation of glycemia (16). However, in individuals with type 1 diabetes, there is often a deficiency of the counterregulatory response, hindering their ability to avoid hypoglycemic events. Moreover, as people with diabetes experience an increased number of episodes of hypoglycemia, the risk of hypoglycemia unawareness, impaired glucose counterregulation (for example, in hypoglycemia-associated autonomic failure [17]), and level 2 and level 3 hypoglycemia (see DEFINITION under HYPOGLYCEMIA) all increase (18). Therefore, it is important to recognize and treat all hypoglycemic events in people with type 1 diabetes, particularly in populations (children, the elderly) that may not have the ability to recognize and self-treat hypoglycemia.

More notable clinical symptoms begin at blood glucose levels <54 mg/dL (3.0 mmol/L) (19,20). As the body's primary utilizer of glucose, the brain is particularly sensitive to decreases in blood glucose concentrations. Both experimental and clinical evidence has shown that, at these levels, neurogenic and neuroglycopenic symptoms including impairments in reaction times, information processing, psychomotor function, and executive function begin to emerge. These neurological symptoms correlate to altered brain activity in multiple brain areas including the prefrontal cortex and medial temporal lobe (21–24). At these levels, individuals may experience confusion, dizziness, blurred or double vision, tremors, and tingling sensations (25). Hypoglycemia at this glycemic level may also increase proinflammatory and prothrombotic markers (26). Left untreated, these symptoms can become severe to the point that an individual will require assistance from others to move or function. Prolonged untreated hypoglycemia that continues to drop below 50 mg/dL (2.8 mmol/L) increases the risk of seizures, coma, and death (27,28). Hypoglycemia that affects cognition and stamina may also increase the risk of accidents and falls, which is a particular concern for older adults with diabetes (29,30).

The glycemic thresholds at which these symptoms occur, as well as the severity with which they manifest themselves, may vary in individuals with type 1 diabetes depending on the number of hypoglycemic episodes they have experienced (31–33). Counterregulatory physiological responses may evolve in patients with type 1 diabetes who endure repeated hypoglycemia over time (34,35).

Definition

The Steering Committee defined three levels of hypoglycemia, as shown in Table 2. These levels are slight modifications to and will update the recently published ADA/EASD position statement (36).

Level 1

Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a marker of physiological hypoglycemia in humans, as it approximates the glycemic threshold for neuroendocrine responses to falling glucose levels in individuals without diabetes. As such, blood glucose in individuals without diabetes is generally 70–100 mg/dL (3.9–5.6 mmol/L) upon waking and 70–140 mg/dL (3.9–7.8 mmol/L) after meals, and any excursions beyond those levels are typically countered with physiological controls (16,37). However, individuals with diabetes who have impaired or altered counterregulatory hormonal and neurological responses do not have the same internal regulation as individuals without diabetes to avoid dropping below 70 mg/dL (3.9 mmol/L) and becoming hypoglycemic. Recurrent episodes of hypoglycemia lead to increased hypoglycemia unawareness, which can become dangerous as individuals cease to experience symptoms of hypoglycemia, allowing their blood glucose levels to continue falling. Therefore, glucose levels <70 mg/dL (3.9 mmol/L) are clinically important, independent of the severity of acute symptoms.

Table 1—Summary of consensus definitions

Outcome	Definition
Hypoglycemia	Level 1: glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L) Level 2: glucose <54 mg/dL (3.0 mmol/L) Level 3: a severe event characterized by altered mental and/or physical status requiring assistance
Hyperglycemia	Level 1—elevated glucose: glucose >180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L) Level 2—very elevated glucose: glucose >250 mg/dL (13.9 mmol/L)
Time in range	Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time
DKA	Elevated serum or urine ketones (greater than the upper limit of the normal range) and serum bicarbonate <15 mmol/L or blood pH <7.3

Table 2—Levels of hypoglycemia

Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

Level 2

Level 2 hypoglycemia is defined as a measurable glucose concentration <54 mg/dL (3.0 mmol/L) that needs immediate action. At ~54 mg/dL (3.0 mmol/L), neurogenic and neuroglycopenic hypoglycemic symptoms begin to occur, ultimately leading to brain dysfunction at levels <50 mg/dL (2.8 mmol/L) (19,20). Neuroglycopenic symptoms—including behavioral changes, visual changes, seizure, and loss of consciousness—are the result of central nervous system neuronal glucose deprivation (21–23).

Level 3

Level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical status requiring assistance. Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia impact a patient to such a degree that the patient requires assistance from others (27,28). Level 3 hypoglycemia is not mutually exclusive from level 1 or level 2. The Steering Committee considered it important to classify "altered mental and/or physical status requiring assistance" as its own category of hypoglycemia given that there are individuals who are able to function independently at a blood glucose <54 mg/dL (3.0 mmol/L) and therefore should not be grouped into the same category as those individuals who require third-party assistance. It is also important to include language on the need for third-party assistance as part of the definition for hypoglycemia, but the term "assistance" is subjective and needs to be clear to allow for evaluation. Including an "altered mental and/or physical status requiring assistance" clarifies the state that the individual is in when necessitating help to correct a low blood glucose value.

In addition to the glucose levels and signs included in the definitions, other specific signs or symptoms of hypoglycemia are important for consideration of individuals with hypoglycemia unawareness and variations in the presentation of hypoglycemia among different demographics. Hypoglycemia that sets in relatively rapidly, such as in the case of a significant insulin overdose, may induce level 2 or level 3 hypoglycemia with little warning (38).

Gaps in Evidence and Measurement

Currently, there is no consistent approach to collecting glucose data that would allow for the appropriate measurement of hypoglycemia. Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) are useful, but not perfect, and their results provide distinct information; one is a point-in-time measurement and the other is a continuous view into changes in glucose levels. Further, CGM can be useful for capturing hypoglycemia missed by SMBG, especially at night, and also for capturing time spent in hypoglycemia. The differences in the methodology and timing used for obtaining blood glucose readings are a challenge for interpreting clinical trial and real-world patient data. Given the differences in the outputs from SMBG and CGM, researchers and clinicians need to determine how the results are interpreted and when the blood glucose level requires a corrective action. The advent of additional information, including trending indicators on CGM devices (39), increases decision-making, as one must decide at what point to correct versus waiting for a low blood glucose to potentially increase. Additionally, there is no consensus on how long an individual must remain at a particular blood glucose level to be considered in the level 1 or level 2 hypoglycemic range (8). Much of the evidence on hypoglycemia to date has been obtained through conventional monitoring; the increased use of CGM and other technologies may provide more insights on these questions.

Therefore, new surveillance methods that provide consistent ways of reporting hypoglycemia should be developed to ensure adequate assessment of the impact of any intervention to prevent and treat the short-term effects of hypoglycemia, including the potential for death. More information on the impact of level 1 and level 2 hypoglycemia—both physiologically and with regard to impairment in how patients feel and function—is needed. Additionally, more work can be done on the links between level 1 and level 2 hypoglycemia to long-term outcomes, as well as the underlying factors of hypoglycemia-associated autonomic failure and other changes to physiological responses to repeated hypoglycemia over time.

HYPERGLYCEMIA

The Diabetes Control and Complications Trial (DCCT) proved that chronic hyperglycemia, as measured by a high HbA_{1c}, is a risk factor for microvascular complications, including retinopathy, nephropathy, and neuropathy (40). The DCCT follow-up study—Epidemiology of Diabetes Interventions and Complications (EDIC)—confirmed the findings of the DCCT and showed that chronic hyperglycemia also increases risk of nonfatal myocardial infarction, stroke, and death from cardiovascular disease (41). Other epidemiological evidence indicates that elevated blood glucose increases cardiovascular risk even in individuals without diabetes (42). The data regarding the effects of chronic hyperglycemia on long-term outcomes is conclusive, indicating that chronic hyperglycemia is a major contributor to morbidity and mortality in type 1 diabetes (41,43–45). The DCCT and subsequent studies have shown that intensive glucose management early in the life of people with type 1 diabetes can have long-lasting beneficial outcomes (46).

Although the correlation between long-term poor glucose control and type 1 diabetes complications is well established, the impact of short-term hyperglycemia is not as well understood. However, hyperglycemia has been shown to have physiological effects and in an acute-care setting is linked to morbidity and mortality in people with and without diabetes. Short-term hyperglycemia, regardless of diabetes diagnosis, has been shown to reduce survival rates among patients admitted to the hospital with stroke or myocardial infarction (47,48). In addition to increasing mortality, short-term hyperglycemia is correlated

with stroke severity and poststroke disability (49,50).

The effects of short-term hyperglycemia have also been observed in nonacute settings. Evidence indicates that hyperglycemia alters retinal cell firing through sensitization in patients with type 1 diabetes (51). This finding is consistent with similar findings showing increased oxygen consumption and blood flow in the retina during hyperglycemia. Because retinal cells absorb glucose through an insulin-independent process, they respond more strongly to increases in glucose in the blood than other cells in patients with type 1 diabetes. The effects of acute hyperglycemia on retinal response may underlie part of the development of retinopathy known to be a long-term complication of type 1 diabetes.

Reports of glucose profiles in individuals without diabetes may provide information to help define normal glucose ranges. For healthy individuals, data indicate that peak postmeal glucose values generally do not exceed 140 mg/dL (7.8 mmol/L) (52). However, other evidence indicates that the majority of individuals without diabetes have blood glucose values that exceed 140 mg/dL (7.8 mmol/L) every day (53,54). In one study, 93% of healthy participants spent time above 140 mg/dL (7.8 mmol/L) with median time above 140 mg/dL (7.8 mmol/L) at 26 min (range 0 min to 6 h 52 min) per day (53). This same study also found that nearly 10% of individuals without diabetes had blood glucose values that reach 200 mg/dL (11.1 mmol/L) during the day, which, by some standards, would be considered indicative of diabetes. Other studies suggest similar glucose patterns for individuals with normal glucose tolerance. A study in 32 individuals with confirmed normal glucose tolerance found that seven participants (22%) reached glucose concentrations >200 mg/dL (11.1 mmol/L) during an average of 28 days of CGM and that participants spent on average 42 min/day at glucose concentrations >140 mg/dL (7.8 mmol/L) (54). In contrast, glucose profiles for individuals with type 1 diabetes and type 2 diabetes demonstrated that glucose concentrations were >140 mg/dL (7.8 mmol/L) during ~60% of the total day or >180 mg/dL (10.0 mmol/L) during ~30% of the total day (52).

Pre- and postmeal glucose targets, approximating glycemic profiles of individuals without diabetes, are used in clinical practice to try to reduce exposure to hyperglycemia. Although specific goals are expected to vary based on individual needs, the ADA guidelines for individuals with diabetes (type 1 and type 2) indicate that premeal blood glucose should be between 80 and 130 mg/dL (4.4 and 7.2 mmol/L) and that peak postprandial glucose should be <180 mg/dL (10.0 mmol/L) (55). AACE guidelines for people with diabetes (type 1 and type 2) suggest that to achieve an HbA_{1c} of ≤6.5% (48 mmol/mol), premeal blood glucose may need to be <110 mg/dL (6.1 mmol/L) and 2-h postmeal blood glucose may need to be <140 mg/dL (7.8 mmol/L) (56,57). These levels represent ideal targets within a near-normal range, as a patient with diabetes may have large fluctuations in glucose levels in real time. All guidelines discuss the need to individualize therapy and create targets that are appropriate for each patient.

Definition

The Steering Committee defines hyperglycemia for individuals with type 1 diabetes as the following:

- Level 1—elevated glucose: glucose >180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L)
- Level 2—very elevated glucose: glucose >250 mg/dL (13.9 mmol/L)

Level 1

Elevated glucose is defined as a glucose concentration >180 mg/dL (10.0 mmol/L) but ≤250 mg/dL (13.9 mmol/L). In clinical practice, measures of hyperglycemia differ based on time of day (e.g., pre- vs. postmeal). This program, however, focused on defining outcomes for use in product development that are universally applicable. Glucose profiles and postprandial blood glucose data for individuals without diabetes suggest that 140 mg/dL (7.8 mmol/L) is the appropriate threshold for defining hyperglycemia. However, data demonstrate that the majority of individuals without diabetes exceed this threshold every day. Moreover, people with diabetes spend >60% of their day above this threshold, which suggests that 140 mg/dL (7.8 mmol/L) is too low of a threshold for measuring hyperglycemia in individuals with diabetes. Current clinical guidelines for people with diabetes indicate that peak prandial glucose should not exceed 180 mg/dL (10.0 mmol/L). As such, the Steering Committee identified 180 mg/dL (10.0 mmol/L) as the initial threshold defining elevated glucose.

Level 2

Very elevated glucose is defined as a glucose concentration >250 mg/dL (13.9 mmol/L). Evidence examining the impact of hyperglycemia does not examine the incremental effects of increasing blood glucose. However, blood glucose values exceeding 250 mg/dL (13.9 mmol/L) increase the risk for DKA (58), and HbA_{1c} readings at that level have been associated with a high likelihood of complications.

Although hyperglycemia is often recognized at different levels depending on a number of circumstances, the above definition allows for the assessment of the ability of therapies and technologies to provide better glucose outcomes and to limit exposure to level 1 and level 2 hyperglycemic blood glucose values. The definition is meant to apply generally to people with type 1 diabetes at any given moment of the day. Further differentiating between blood glucose values >250 mg/dL (13.9 mmol/L) is less likely to be clinically meaningful except in instances of hyperglycemic hyperosmolar syndrome. For this reason, hyperglycemia is best defined with a two-category classification.

Gaps in Evidence and Measurement

Further research is needed to better understand the effects of individual episodes of hyperglycemia as opposed to sustained hyperglycemia over time. More research would be helpful for understanding the connections between hyperglycemia and macrovascular disease and other chronic complications, including the role of genetic factors and a patient's ability to recognize when hyperglycemia is occurring. This research is complicated by the fact that many patients with type 1 diabetes naturally have sustained hyperglycemia; CGM may benefit from such research. Also, more work can be done to elucidate any genetic variables that would affect physiological responses to hyperglycemia. PROs that address the impact of hyperglycemia for patients are also needed, as will be discussed in a later section.

TIME IN RANGE

An individual whose blood glucose levels rarely extend beyond the thresholds

defined for hypo- and hyperglycemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It is also evident that if the intent of a given intervention is to safely manage blood glucose but the intervention does not reliably maintain blood glucose within safe levels, then the intervention should not be considered effective.

The time in range outcome is distinguished from traditional HbA_{1c} testing in several ways (4,59). Time in range captures fluctuations in glucose levels continuously, whereas HbA_{1c} testing is done at static points in time, usually months apart (60). Furthermore, time in range is more specific and sensitive than traditional HbA_{1c} testing; for example, a treatment that addresses acute instances of hypo- or hyperglycemia may be detected in a time in range assessment but not necessarily in an HbA_{1c} assessment. As a percentage, time in range is also more likely to be comparable across patients than HbA_{1c} values, which are more likely to have patient-specific variations in significance (61). Finally, time in range may be more likely than HbA_{1c} levels to correlate with PROs, such as quality of life, because the outcome is more representative of the whole patient experience (62). Table 3 illustrates how the concept of time in range differs from current HbA_{1c} testing.

Nevertheless, evidence describing the negative effects of hypo- and hyperglycemia does not directly demonstrate the positive effects of maintaining blood glucose between those two thresholds. For example, evidence may point to health outcomes being optimal if time in range is defined at thresholds that are narrower than the hypo- and hyperglycemia thresholds. Also, variation in what is considered "normal" glucose fluctuations across populations, as well as what is realistically achievable for people with type 1 diabetes, must be taken into account so as not to make the target range definition too restrictive. In addition, as discussed in HYPERGLYCEMIA, clinical guidelines include pre- and postmeal glucose targets underscoring the importance of a target range.

At least one study has demonstrated the direct clinical relevance of time in range correlating to positive overall outcomes. This prospective inpatient study evaluated 227 patients (100 with type 2 diabetes and 127 without diabetes) post–cardiac surgery to assess glucose control. For the purposes of this study, time in range was defined as being time in the range of 108–146 mg/dL (6.0–8.1 mmol/L). Patients received insulin to target glucose concentrations within that range. The results of the study showed that post–cardiac surgery patients with 80% of time within a range of 108–146 mg/dL (6.0–8.1 mmol/L) had better outcomes, with or without diabetes, compared with patients with less than 80%. While the factors influencing inpatient recovery are varied, the study suggests a correlation between positive outcomes and time in range (63). Other research has indicated a link between a high percentage of time in range with recovery of glucose counterregulation and hypoglycemia symptom recognition in patients with type 1 diabetes following intrahepatic islet transplantation (64).

Table 3—HbA_{1c} testing and time in range outcome

HbA_{1c} testing	Time in range outcome
Evaluates single HbA_{1c} levels	Evaluates continuous glucose levels
Compares HbA_{1c} levels 3 months apart	May compare fluctuations for any given amount of time
Does not capture hypoglycemic or hyperglycemic levels occurring in the same day	Captures all glucose levels for the given time frame and identifies time within a safe range
Less likely to capture impact of acute interventions	Likely to capture impact of acute interventions

More commonly, time in range has been adopted by researchers evaluating the precision and effectiveness of emerging glucose monitoring and automated insulin delivery technologies. None of these studies relate time in range to any long-term diabetes outcomes, as these studies are of short duration. In one example, researchers compared a wearable, bihormonal, automated device to an insulin pump for 5 days over a 96-h period in 52 adults and adolescents with type 1 diabetes. Researchers measured the percent time in range by the hour, and the desired glucose range was defined as 70–180 mg/dL (3.9–10.0 mmol/L). They demonstrated that the bihormonal device was able to keep patients within a range of 70–180 mg/dL (3.9–10.0 mmol/L) for more time than the insulin pump, concluding that this device was a more effective means of managing blood glucose (65).

Definition

The Steering Committee defines time in range for individuals with type 1 diabetes as the following:

- Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time

The Steering Committee considered it important to keep the time in range definition wide in order to accommodate variations across the population with type 1 diabetes—including different age-groups—but limited enough to preclude the possibility of negative outcomes. The upper and lower bounds of the time in range definition are consistent with the definitions for hypo- and hyperglycemia defined above. For individuals without type 1 diabetes, 70–140 mg/dL (3.9–7.8 mmol/L) represents a normal glycemic range (66). However, spending most of the day in this range is not generally achievable for people with type 1 diabetes because they do not have physiological insulin secretion (67). The current postprandial blood glucose target for people with type 1 diabetes is 180 mg/dL (10.0 mmol/L), and, as such, an upper limit of 180 mg/dL (10.0 mmol/L) allows the definition to be applied across the broad population with type 1 diabetes (55).

The Steering Committee noted that, to date, the use of time in range has been to test the effectiveness of technologies designed to monitor blood glucose levels in real time and maintain glucose control. In order to generate the data necessary to measure time in range, CGM or similar technologies must be used. Use of CGM among the population with type 1 diabetes has been suggested to be ~11% in some populations and increasing in adoption rate (1). The Steering Committee felt that these technologies were at a point of development in which they could and should be used safely and effectively to capture time in range data.

Gaps in Evidence and Measurement

To date, there is limited research correlating time in range with positive short-term

and long-term type 1 diabetes outcomes, as opposed to the extensive research demonstrating the negative consequences of excursions into hyper- or hypoglycemia. More substantial evidence demonstrating a correlation or a direct causative relationship between time in range for patients with type 1 diabetes and positive health outcomes is needed.

Variations across the literature that examined time in range included differences in glycemic variability, dietary factors, sample sizes, and population demographics that will need to be reconciled as further research develops. A deficiency in evidence for the pediatric population was noted (67,68). Members of the committee noted that more evidence could be gathered on the experience of individuals with type 1 diabetes both in and out of glycemic range, which would potentially be captured in a PRO, as will be described later in this article.

DKA

DKA is often associated with hyperglycemia. In most cases, in an individual with diabetes, the cause of hyperglycemia is also the cause of DKA, although the two conditions are distinct. DKA develops when a lack of glucose in cells prompts the body to begin breaking down fatty acid reserves. This increases the levels of ketones in the body (ketosis) and causes a drop in blood pH (acidosis). At its most severe, DKA can cause cerebral edema, acute respiratory distress, thromboembolism, coma, and death (69,70).

The details of how DKA induces near-term physiological effects, as well as how it may potentially contribute to long-term complications, continue to be researched. Evidence suggests that DKA causes acute negative effects on the myocardium in adults and children, as indicated by increases of troponin I concentrations under DKA conditions (71).

DKA was found to be consistently characterized across studies. In part, this consistency was due to the well-known clinical effects of ketoacidosis, particularly low blood pH. Where definitions varied, the discrepancies are predominantly seen in minor changes to the range of what was considered mild or severe.

Definition

Although the current definition for DKA includes a list of multiple criteria that must be met, not all information currently included in the accepted definition is consistently gathered or required to diagnose DKA. The Steering Committee defines DKA in individuals with type 1 diabetes in a clinical setting as the following:

- Elevated serum or urine ketones (greater than the upper limit of the normal range), and
- Serum bicarbonate $<$15 mmol/L or blood pH $<$7.3

Given the seriousness of DKA, it is unnecessary to stratify DKA into different levels or categories, as the presence of DKA—regardless of the differences observed in the separate biochemical tests—should always be considered serious. In individuals with known diabetes, plasma glucose values are not necessary to diagnose DKA. Further, new therapeutic agents, specifically sodium–glucose cotransporter 2 inhibitors, have been linked to euglycemic DKA, or DKA with blood glucose values $<$250 mg/dL (13.9 mmol/L). Numerical values for urine or serum ketones are not specified in the DKA definition due to the variation in assay normal ranges across laboratory settings.

Gaps in Evidence and Measurement

DKA is a well-understood condition with well-recognized signs and symptoms. The current evidence is sufficient to support the definition described. Nevertheless, additional studies are needed to establish more definitive information about the effects of DKA and of recurrent DKA over time, including connections to vascular and cognitive complications. This limitation in research is likely due to studies of patients with DKA typically beginning only once patients are admitted to the hospital. There is also no evidence to suggest that there is a "safe" or benign amount of time to experience DKA; this may be a question worth exploring as, for example, varying degrees of DKA severity might have different long-term outcomes.

PROs

In guidance released in 2009 (72), the U.S. Food and Drug Administration (FDA) defined PROs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." In the same document, the FDA clearly acknowledged the importance of PROs, advising that they be used to gather information that is "best known by the patient or best measured from the patient perspective."

Measuring and using PROs is increasingly seen as essential to evaluating care from a patient-centered perspective, which is a key aspect of health care reform efforts under the National Quality Strategy (73). PROs can capture information helpful for guiding diabetes care teams on which aspects of their care delivery they need to improve (74). Stakeholders have advocated for the inclusion of PROs as a component of a complete diabetes measure portfolio (75).

Given that type 1 diabetes is a chronic condition primarily treated on an outpatient basis, much of what people with type 1 diabetes experience is not captured through standard clinical measurement. Measures that capture PROs can fill these important information gaps. A variety of validated measures (including surveys and questionnaires) of some PROs for youth and adults with type 1 diabetes are available and are used in clinical studies, including those for diabetes distress (76) and fear of hypoglycemia (77). Work to further develop and validate tools and measures for diabetes health-related quality of life is ongoing.

Gaps in Measurement and Evidence

The use of validated PROs in type 1 diabetes clinical research is not currently widespread, and challenges to effectively measuring some PROs, such as quality of life, continue to confront researchers and developers. While many studies of type 1 diabetes treatments, including devices, in some way assess PROs (78,79), further work is needed to develop standard PROs for type 1 diabetes, including assessments of burden to patients. Such measures would need to be applicable across and between age ranges, settings, and over multiple years to evaluate trends in order to be relevant at the clinical trial level.

CONCLUSIONS

The Steering Committee developed definitions for outcomes beyond HbA_{1c} in type 1 diabetes including hypoglycemia, hyperglycemia, time in range, and DKA. These definitions were based on relevant published evidence and the clinical experience and expertise of the Steering Committee representatives and members of the Advisory Committees.

Knowledge gaps, including around PROs, were identified and should be addressed by future research. The Steering Committee recommends use of the defined clinically meaningful outcomes beyond HbA_{1c} in the research, development, and evaluation of type 1 diabetes therapies.

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