Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes

Matthew C. Riddle,[1] William T. Cefalu,[2] Philip H. Evans,[3] Hertzel C. Gerstein,[4] Michael A. Nauck,[5] William K. Oh,[6] Amy E. Rothberg,[7] Carel W. le Roux,[8] Francesco Rubino,[9] Philip Schauer,[10] Roy Taylor,[11] and Douglas Twenefour[12]

Diabetes Care 2021;44:2438–2444 | https://doi.org/10.2337/dci21-0034

CONSENSUS REPORT

Improvement of glucose levels into the normal range can occur in some people living with diabetes, either spontaneously or after medical interventions, and in some cases can persist after withdrawal of glucose-lowering pharmacotherapy. Such sustained improvement may now be occurring more often due to newer forms of treatment. However, terminology for describing this process and objective measures for defining it are not well established, and the long-term risks versus benefits of its attainment are not well understood. To update prior discussions of this issue, an international expert group was convened by the American Diabetes Association to propose nomenclature and principles for data collection and analysis, with the goal of establishing a base of information to support future clinical guidance. This group proposed "remission" as the most appropriate descriptive term, and HbA_{1c} <6.5% (48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy as the usual diagnostic criterion. The group also made suggestions for active observation of individuals experiencing a remission and discussed further questions and unmet needs regarding predictors and outcomes of remission.

The natural history of type 2 diabetes (T2D) is better understood now than previously. It is clearly heterogeneous, with both genetic and environmental factors contributing to its pathogenesis and evolution. Typically, a genetic predisposition is present at birth but the hyperglycemia that defines diabetes appears only gradually and reaches diagnostic levels in adulthood. Environmental factors modulating expression of T2D include availability of various foods; opportunity for and participation in physical activity; stress related to family, work, or other influences; exposure to pollutants and toxins; and access to public health and medical resources. Two common but transitory events can lead to earlier emergence of hyperglycemia in susceptible individuals: pregnancy or short-term therapy with glucocorticoids. Accordingly, people may develop "gestational diabetes" or "steroid diabetes" as conditions that are distinct but nevertheless related to typical T2D (1,2). In these settings, hyperglycemia is provoked by insulin resistance but may not persist, as responses to insulin improve when the baby is delivered or glucocorticoid therapy ceases. Glucose levels can return to normal after the pregnancy, yet an increased risk of later T2D remains (3). Acute illness or other stressful experiences can also provoke temporary hyperglycemia, sometimes called "stress hyperglycemia," in vulnerable individuals. T2D that has developed gradually and independent of these stimuli, but most often accompanying weight gain in midlife, can become easier to control or appear to remit following weight loss in some cases. Moreover, individuals with T2D can unintentionally lose weight due to illness, emotional distress, or unavailability of food related to serious social dislocation. Either voluntary or

[1]*Division of Endocrinology, Diabetes, & Clinical Nutrition, Department of Medicine, Oregon Health & Science University, Portland, OR*
[2]*Division of Diabetes, Endocrinology and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*
[3]*College of Medicine and Health, University of Exeter, Exeter, U.K.*
[4]*Population Health Research Institute and Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada*
[5]*Diabetes Division, Katholisches Klinikum Bochum gGmbH, St. Josef-Hospital, Ruhr University Bochum, Bochum, Germany*
[6]*Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*
[7]*Department of Internal Medicine, Michigan Medicine, and Department of Nutritional Sciences, School of Public Health, University of Michigan, Ann Arbor, MI*
[8]*Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland*
[9]*Department of Diabetes, School of Life Course Sciences, King's College London, London, U.K.*
[10]*Pennington Biomedical Research Center, Baton Rouge, LA*
[11]*Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, U.K.*
[12]*Diabetes UK, London, U.K.*

Corresponding author: Matthew C. Riddle, riddlem@ohsu.edu

Received 17 June 2021 and accepted 17 June 2021

This Consensus Report is jointly published in The Journal of Clinical Endocrinology & Metabolism*, published by Oxford University Press on behalf of the Endocrine Society;* Diabetologia*, published by Springer-Verlag, GmbH, on behalf of the European Association for the Study of Diabetes;* Diabetic Medicine*, published by Wiley on behalf of Diabetes UK; and* Diabetes Care*, published by the American Diabetes Association.*

A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel (i.e., consensus panel) and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/

unexpected decline of weight in T2D may allow or require cessation of glucose-lowering treatment.

These changing patterns of glycemia have important epidemiologic implications. One is that T2D can remit without specific intervention in some cases. Another is that complications specific to diabetes, such as diabetic glomerulopathy, can be found in people without concurrent diabetes who were exposed to chronic hyperglycemia in the past (4). Yet another is a U-shaped relationship between glucose levels and death in T2D, with increased risk at normal or lower levels of hemoglobin A_{1c} (HbA_{1c}). This pattern might be attributed to overtreatment of T2D, leading to an increased risk of hypoglycemia (5), but alternatively could result from weight loss and declining glucose levels due to another serious and potentially fatal illness (6). Thus, both sustained increases and sustained decreases of glucose levels can occur spontaneously or through interventions and can present problems of interpretation.

Therapies targeting metabolic control in T2D have improved greatly in recent years. Short-term pharmacologic therapy at the time of first presentation of T2D in adults can sometimes restore nearly normal glycemic control, allowing therapy to be withdrawn (7–9). Reversal of "glucose toxicity" accompanying restoration of glycemic control is best documented with early intensive insulin therapy but can occur with other interventions. New classes of drugs, the glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter inhibitors, can sometimes attain excellent glycemic control with little tendency to cause hypoglycemia. Significant behavioral changes—mainly related to nutrition and weight management—can lead to a return from overt hyperglycemia to nearly normal glucose levels for extended periods of time (10,11). More dramatically, surgical or other enteral interventions can induce both significant weight loss and further improvement of metabolic control by other mechanisms for prolonged periods (12–14)—5 years or more in some cases. A return to nearly normal glycemic regulation after all these forms of intervention is most likely early in the course of T2D and can involve partial recovery of both insulin secretion and insulin action (15).

Increasingly, experience with sustained improvement of glucose levels into the normal range has prompted a reevaluation of terminology and definitions that may guide current discussions and future research in managing such transitions in glycemia in T2D. In 2009 a consensus statement initiated by the American Diabetes Association (ADA) addressed these issues (16). It suggested that "remission," signifying "abatement or disappearance of the signs and symptoms," be adopted as a descriptive term. Three categories of remission were proposed. "Partial" remission was considered to occur when hyperglycemia below diagnostic thresholds for diabetes was maintained without active pharmacotherapy for at least 1 year. "Complete" remission was described as normal glucose levels without pharmacotherapy for 1 year. "Prolonged" remission could be described when a complete remission persisted for 5 years or more without pharmacotherapy. A level of HbA_{1c} <6.5% (<48 mmol/mol) and/or fasting plasma glucose (FPG) 100–125 mg/dL (5.6 to 6.9 mmol/L) were used to define a partial remission, while "normal" levels of HbA_{1c} and FPG (<100 mg/dL [5.6 mmol/L]) were required for a complete remission.

To build upon this statement and subsequent publications (17) in the context of more recent experience, the ADA convened an international, multidisciplinary expert group. Representatives from the American Diabetes Association, European Association for the Study of Diabetes, Diabetes UK, the Endocrine Society, and the Diabetes Surgery Summit were included. For another perspective, an oncologist was also part of the expert group. This group met three times in person and conducted additional electronic exchanges between February 2019 and September 2020. The following is a summary of these discussions and conclusions derived from them. This report is not intended to establish treatment guidelines or to favor specific interventions. Instead, based on consensus reached by the authors, it proposes suitable definitions of terms and ways to assess glycemic measurements, to facilitate collection and analysis of data that may lead to future clinical guidance.

OPTIMAL TERMINOLOGY

The choice of terminology has implications for clinical practice and policy decisions. Several terms have been proposed for people who have become free of a previously diagnosed disease state. In T2D, the terms *resolution*, *reversal*, *remission*, and *cure* each have been used to describe a favorable outcome of interventions resulting in a disease-free status. In agreement with the prior consensus group's conclusions (16), this expert panel concluded that diabetes *remission* is the most appropriate term. It strikes an appropriate balance, noting that diabetes may not always be active and progressive yet implying that a notable improvement may not be permanent. It is consistent with the view that a person may require ongoing support to forestall relapse, and regular monitoring to allow intervention should hyperglycemia recur. Remission is a term widely used in the field of oncology (18), defined as a decrease in or disappearance of signs and symptoms of cancer.

A common tendency is to equate remission with "no evidence of disease," allowing a binary choice of diagnosis. However, diabetes is defined by hyperglycemia, which exists on a continuum. The consensus group concluded that "no evidence of diabetes" was not an appropriate term to apply to T2D. One reason for this decision was that

or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight gaps in evidence and propose areas of future research to address these gaps. A consensus report is not an American Diabetes Association (ADA) position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

the underlying pathophysiology of T2D, including both deficiency of insulin and resistance to insulin's actions, as well as other abnormalities, is rarely completely normalized by interventions (19–21). In addition, any criterion for identifying a remission of diabetes will necessarily be arbitrary, a point on a continuum of glycemic levels. Although the previous consensus statement suggested dividing diabetes remission into partial and complete categories, using different glycemic thresholds (16), this distinction could introduce ambiguity affecting policy decisions related to insurance premiums, reimbursements, and coding of medical encounters. The prior statement's suggestion that a prolonged remission, longer than 5 years, be considered separately did not have an objective basis. The present group doubted that this distinction would assist clinical decisions or processes, at least until more objective information about the frequency of long-term remissions and the medical outcomes associated with them is available. A single definition of remission based on glycemic measurements was thought more likely to be helpful.

The other candidate terms have limitations. Considering a diagnosis of diabetes to be *resolved* suggests either that the original diagnosis was in error or that an entirely normal state has been permanently established. The term *reversal* is used to describe the process of returning to glucose levels below those diagnostic of diabetes, but it should not be equated with the state of remission. The term *cure* seems especially problematic in suggesting that all aspects of the condition are now normalized and that no clinical follow-up or further management will be needed either for a recurrence of hyperglycemia or for additional risks associated with the underlying physiological abnormalities. While cure is a hoped-for outcome, as in cancer patients, the group agreed that the term should be avoided in the context of T2D.

GLYCEMIC CRITERIA FOR DIAGNOSING REMISSION OF T2D

Measures widely used for diagnosis or glycemic management of T2D include HbA_{1c}, FPG, 2-h plasma glucose after an oral glucose challenge, and mean daily glucose as measured by continuous glucose monitoring (CGM). The group favored HbA_{1c} below the level currently used for initial diagnosis of diabetes, 6.5% (48 mmol/mol), and remaining at that level for at least 3 months without continuation of the usual antihyperglycemic agents as the main defining measurement. Methods used to measure HbA_{1c} must have stringent quality assurance in place and assays must be standardized to criteria aligned to international reference values (22–24).

However, a number of factors can affect HbA_{1c} measurements, including a variant hemoglobin, differing rates of glycation, or alterations of erythrocyte survival that can occur in a variety of disease states. Information on which methods are affected by variant hemoglobins can be found at http://ngsp.org/interf.asp. Thus, in some people a normal HbA_{1c} value may be present when glucose is actually elevated, or HbA_{1c} may be high when mean glucose is normal. In settings where HbA_{1c} may be unreliable, measurement of 24-h mean glucose concentrations by CGM has been proposed as an alternative. A glycated hemoglobin value calculated as equivalent to the observed mean glucose by CGM has been termed the estimated HbA_{1c} (eA1C) (25) or most recently a glucose management indicator (GMI) (26). In cases where the accuracy of HbA_{1c} values is uncertain, CGM can be used to assess the correlation between mean glucose and HbA_{1c} and identify patterns outside the usual range of normal (27,28).

An FPG lower than 126 mg/dL (7.0 mmol/L) can in some settings be used as an alternate criterion for remission, just as a value higher than that level is an alternative for initial diagnosis of T2D. This approach has the disadvantage of requiring sample collection while fasting overnight, together with significant variation between repeated measurements. Testing of 2-h plasma glucose following a 75-g oral glucose challenge seems a less desirable choice, in part because of the added complexity of obtaining it and the high variability between repeated measurements. In addition, metabolic surgical interventions can alter the usual patterns of glycemic response to oral glucose, with early hyperglycemia followed by later hypoglycemia after an oral glucose challenge, further confounding interpretation of the test.

Considering all alternatives, the group strongly favored use of HbA_{1c} $<6.5\%$ (48 mmol/mol) as generally reliable and the simplest and most widely understood defining criterion under usual circumstances. In some circumstances, an eA1C or GMI $<6.5\%$ can be considered an equivalent criterion.

CAN REMISSION BE DIAGNOSED WHILE GLUCOSE-LOWERING DRUGS ARE BEING USED?

Diabetes remission may be achieved by a change of lifestyle, other medical or surgical interventions, or—as is often the case—a combination of these approaches. Whether a therapy needs to be discontinued before making a diagnosis of remission depends on the intervention. Alterations of lifestyle involving day-to-day routines related to nutrition and physical activity have health effects that extend well beyond those related to diabetes. Moreover, the possibility of not only achieving diabetes remission but also generally improving health status may have motivated the individual to make these changes in the first place. These considerations also apply to surgical approaches, which, in addition, are not easily reversed. A remission can therefore be diagnosed postoperatively and in the setting of ongoing lifestyle efforts.

Whether a remission can be diagnosed in the setting of ongoing pharmacotherapy is a more complex question. In some cases, excellent glycemic control can be restored by short-term use of one or more glucose-lowering drugs, with persistence of nearly normal levels even after cessation of these agents. If antihyperglycemic drug therapy continues, it is not possible to discern whether a drug-independent remission has occurred. A diagnosis of remission can only be made after all glucose-lowering agents have been withheld for an interval that is sufficient both to allow waning of the drug's effects and to assess the effect of the absence of drugs on HbA_{1c} values.

This criterion would apply to all glucose-lowering drugs including those with other effects. Notably, metformin might be prescribed for weight maintenance, to improve markers of risk for

cardiovascular disease or cancer, or for the polycystic ovarian syndrome (29). GLP-1 receptor agonists might be favored to control weight or reduce risk of cardiovascular events, and sodium-glucose cotransporter inhibitors may be prescribed for heart failure or renal protection. If such considerations preclude stopping these drugs, then remission cannot be diagnosed even though nearly normal glycemic levels are maintained. A clinical decision may be made to continue such therapies without testing for remission, and in that case, whether a true remission has been attained remains unknown. The group also recognized that some drugs have a modest glucose-lowering effect but are not indicated for glucose lowering, as in the case of some weight loss drugs. Because these drugs are not used to manage hyperglycemia specifically, they would not need to be stopped before a diagnosis of diabetes remission can be made.

Another concern is the possible role of preventive drug intervention for individuals who have been diagnosed with remission or are otherwise known to be at very high risk of T2D, such as women with prior gestational diabetes. Should such individuals be candidates for treatment with antihyperglycemic therapy, especially with metformin? This is a controversial area, with arguments both for and against. In favor of pharmacotherapy to prevent emergence or re-emergence of overt diabetes is the possibility of safely and inexpensively eliminating a period of undiagnosed yet harmful hyperglycemia (30). On the other side is the argument that protection against β-cell deterioration by pharmacotherapy has yet to be convincingly proven and preventive intervention has known costs and potential risks (31).

Whether preventive intervention is justified was thought to be beyond the scope of the present statement, except to note that, if it is used, whether a remission is persisting cannot be known. Data systematically collected based on the definitions proposed in this document may help to clarify the roles of the various interventions that might be used in this setting.

TEMPORAL ASPECTS OF DIAGNOSING REMISSION

When intervention in T2D is by pharmacotherapy or surgery, the time of initiation is easily determined and the clinical effects are rapidly apparent (Table 1). When intervention is by alteration of lifestyle, the onset of benefit can be slower, and up to 6 months may be required for stabilization of the effect. A further temporal factor is the approximately 3 months needed for an effective intervention to be entirely reflected by the change of HbA_{1c}, which reflects mean glucose over a period of several months. Considering these factors, an interval of at least 6 months after initiation of a lifestyle intervention is needed before testing of HbA_{1c} can reliably evaluate the response. After a more rapidly effective surgical intervention, an interval of at least 3 months is required while the HbA_{1c} value stabilizes. When the intervention is with temporary pharmacotherapy, or when a lifestyle or metabolic surgery intervention is added to prior pharmacotherapy, an interval of at least 3 months after cessation of any glucose-lowering agent is required. With all interventions leading to remission, subsequent measurements of HbA_{1c} not more often than every 3 months nor less frequent than yearly are advised to confirm continuation of the remission. In contrast to HbA_{1c}, FPG or eA1C derived from CGM can stabilize at a shorter time after initiation of an intervention, or increase more rapidly if glycemic control worsens later on. When these measurements of glucose are substituted for HbA_{1c}, they can be collected sooner after the intervention and more frequently thereafter, but because they are more variable, a value consistent with onset or loss of a remission should be confirmed by a repeated measurement.

PHYSIOLOGIC CONSIDERATIONS REGARDING REMISSIONS FOLLOWING INTERVENTION WITH PHARMACOTHERAPY, LIFESTYLE, OR METABOLIC SURGERY

When a remission is documented after temporary use of glucose-lowering agents, the direct effects of pharmacotherapy do not persist. Reversal of the adverse effects of poor metabolic control (32) on insulin secretion and action may establish a remission, but other underlying abnormalities persist and the duration of the remission is quite variable. In contrast, when a persistent change of lifestyle leads to remission, the change in food intake, physical activity, and management of stress and environmental factors can favorably alter insulin secretion and action for long periods of time. In this setting, long-term remissions are possible, but not assured. The effects of metabolic surgery are more profound and generally more sustained (33). Structural changes of the gastrointestinal tract lead to a novel hormonal milieu. This includes, among other changes, several-fold greater GLP-1 concentrations in blood after

Table 1—Interventions and temporal factors in determining remission of T2D

Intervention *Note: Documentation of remission should include a measurement of HbA_{1c} just prior to intervention*	Interval before testing of HbA_{1c} can reliably evaluate the response	Subsequent measurements of HbA_{1c} to document continuation of a remission
Pharmacotherapy	At least 3 months after cessation of this intervention	Not more often than every 3 months nor less frequent than yearly
Surgery	At least 3 months after the procedure *and* 3 months after cessation of any pharmacotherapy	
Lifestyle	At least 6 months after beginning this intervention *and* 3 months after cessation of any pharmacotherapy	

eating, which through interaction with relevant areas of the brain may reduce appetite and food intake and additionally alter peripheral metabolism. Re-establishment of glucose homeostasis by these mechanisms is typically longer lasting. The changes of anatomy and physiology are essentially permanent, but even so the desirable effects on glycemic patterns may not be sustained indefinitely. Partial regain of weight can occur, and continuing decline of β-cell capacity may contribute to rising levels of glucose over time.

ONGOING MONITORING

For the reasons just described, a remission is a state in which diabetes is not present but which nonetheless requires continued observation because hyperglycemia frequently recurs. Weight gain, stress from other forms of illness, and continuing decline of β-cell function can all lead to recurrence of T2D. Testing of HbA_{1c} or another measure of glycemic control should be performed no less often than yearly. Ongoing attention to maintenance of a healthful lifestyle is needed, and pharmacotherapy for other conditions with agents known to promote hyperglycemia, especially glucocorticoids and certain antipsychotic agents, should be avoided.

The metabolic memory, or legacy effect (34), is relevant in this setting. These terms describe the persisting harmful effects of prior hyperglycemia in various tissues. Even after a remission, the classic complications of diabetes—including retinopathy, nephropathy, neuropathy, and enhanced risk of cardiovascular disease—can still occur (35). Hence, people in remission from diabetes should be advised to have regular retinal screening, tests of renal function, foot evaluation, and measurement of blood pressure and weight in addition to ongoing monitoring of HbA_{1c}. At present, there is no long-term evidence indicating that any of the usually recommended assessments for complications can safely be discontinued. Individuals who are in remission should be advised to remain under active medical observation including regular check-ups.

In addition to continued gradual progression of established complications of T2D, there is another risk potentially associated with a remission. This is the possibility of an abrupt worsening of microvascular disease following a rapid reduction of glucose levels after a long period of hyperglycemia. In particular, when poor glycemic control is present together with retinopathy beyond the presence of microaneurysms, rapid reduction of glucose levels should be avoided and retinal screening repeated if a rapid decline in blood glucose is observed. This suggestion is based mainly upon experience with worsening of retinopathy after initiation or intensification of insulin therapy, which is seen only if moderate or worse retinopathy is present at baseline (36,37). Worsening of retinopathy can occur with other interventions, although there is some evidence that this risk is less after metabolic surgery (38).

FURTHER QUESTIONS AND UNMET NEEDS

The preceding discussion is based largely on expert opinion. It is not intended to provide guidance regarding how or when glycemic control qualifying as a remission should be sought. It also does not aim to clarify the role of preventive pharmacotherapy after a remission is identified. Rather, it proposes terminology and a structure to facilitate future research and collection of information to support future clinical guidelines. Some of the areas needing further research are listed below.

Validation of Using 6.5% HbA_{1c} as the Defining Measurement

The relative effectiveness of using 6.5% HbA_{1c} (48 mmol/mol) as the cut point for diagnosis of remission, as opposed to 6.0% HbA_{1c} (42 mmol/mol), HbA_{1c} 5.7% (39 mmol/mol), or some other level, in predicting risk of relapse or of microvascular or cardiovascular complications should be evaluated. The use of CGM-derived data to adjust HbA_{1c} target ranges for identifying glycemic remission should be further explored. Use of CGM-derived average glucose judged equivalent to HbA_{1c} $<$6.5% ($<$48 mmol/mol) or use of FPG $<$7.0 mmol/L ($<$126 mg/dL) instead of HbA_{1c} could be studied.

Validation of the Timing of Glycemic Measurements

Less frequent testing of HbA_{1c} might be possible without altering predictive efficiency. For example, routine measurements at 6 months and 12 months might be sufficient to identify remission and risk of relapse in the short term.

Evaluation of the Effects of Metformin and Other Drugs After Remission Is Established

Metformin's main action affecting glycemic control in diabetes is to improve hepatic responsiveness to portal insulin. Whether it can delay relapse through other mechanisms is unknown. After diagnosis of remission, therapy with metformin or other drugs not used for glycemic indications may delay recurrence of hyperglycemia and/or protect against progression of other metabolic disturbances. Objective information on this point is limited, and more research is clearly required.

Evaluation of Nonglycemic Measures During Remission

Improved glycemic control is not the only aspect of metabolism that may affect long-term outcomes. For example, circulating lipoprotein profiles, peripheral and visceral adiposity, and intracellular fat deposition in the liver and other tissues may all be relevant effects accompanying—or possibly separate from—glycemic remission and could be evaluated. The role of changes in GLP-1 and other peptide mediators after pharmacologic, behavioral, or surgical interventions in altering risks of relapse or medical events remains unknown.

Research on Duration of Remission

The expected duration of a remission induced by various interventions is still not well defined, and factors associated with relapse from remission should be examined more fully.

Documentation of Long-term Outcomes After Remission

Long-term effects of remission on mortality, cardiovascular events, functional capacity, and quality of life are unknown. Metabolic and clinical factors related to these outcomes during remission are poorly understood and could be defined.

Development of Educational Materials for Health Care Professionals and Patients

Development and standardization of educational and screening programs for individuals in remission would facilitate

application of various recommendations to clinical practice.

CONCLUSIONS

A return to normal or nearly normal glucose levels in patients with typical T2D can sometimes be attained by using current and emerging forms of medical or lifestyle interventions or metabolic surgery. The frequency of sustained metabolic improvement in this setting, its likely duration, and its effect on subsequent medical outcomes remain unclear. To facilitate clinical decisions, data collection, and research regarding outcomes, more clear terminology describing such improvement is needed. On the basis of our discussions, we propose the following:

1. The term used to describe a sustained metabolic improvement in T2D to nearly normal levels should be *remission* of diabetes.
2. Remission should be defined as a return of *HbA_{1c} to <6.5% (<48 mmol/mol)* that occurs spontaneously or following an intervention and that persists for *at least 3 months* in the absence of usual glucose-lowering pharmacotherapy.
3. When HbA_{1c} is determined to be an unreliable marker of chronic glycemic control, *FPG <126 mg/dL (<7.0 mmol/L)* or *eA1C <6.5%* calculated from CGM values can be used as alternate criteria.
4. Testing of HbA_{1c} to document a remission should be performed just prior to an intervention and no sooner than 3 months after initiation of the intervention and withdrawal of any glucose-lowering pharmacotherapy.
5. Subsequent testing to determine long-term maintenance of a remission should be done at least yearly thereafter, together with the testing routinely recommended for potential complications of diabetes.
6. Research based on the terminology and definitions outlined in the present statement is needed to determine the frequency, duration, and effects on short- and long-term medical outcomes of remissions of T2D using available interventions.

Duality of Interest. M.C.R. reports receiving research grant support through Oregon Health & Science University from Eli Lilly & Co., Novo Nordisk, and AstraZeneca and honoraria for consulting from Adocia, Intercept, and Theracos. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care and reports research grants from Eli Lilly & Co., AstraZeneca, Merck, Novo Nordisk and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Merck, Novo Nordisk, Janssen, Sanofi, and Kowa. M.A.N. has been a member on advisory boards or has consulted for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and Novo Nordisk; has received grant support from AstraZeneca, Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novo Nordisk; and has served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, and Novo Nordisk. W.K.O. reports serving as a consultant to Astellas, AstraZeneca, Bayer, Janssen, Sanofi, and Sema4 and has recently taken a role as Chief Medical Science Officer for Sema4. A.E.R. is a member of the advisory board for Rhythm Pharmaceuticals, Inc. and REWIND Co. C.W.l.R. reports serving on advisory boards and receiving honoraria for speaker meetings from Novo Nordisk, GI Dynamics, Johnson & Johnson, Herbalife, Boehringer Ingelheim, Sanofi, Keyron, and AnBio and has received funding from the EU Innovative Medicine Initiative, Science Foundation Ireland, Health Research Board, Irish Research Council, Swedish Research Council, and European Foundation for Study of Diabetes. F.R. reports receiving research grants from Ethicon and Medtronic and consulting fees from Ethicon, Novo Nordisk, and Medtronic and is on the scientific advisory board of GI Dynamics and Keyron. P.S. received grant support from Ethicon, Medtronic, and Pacira and serves as a consultant for Ethicon, Medtronic, GI Dynamics, Persona, Keyron, Mediflix, SE LLC, and Medscape. R.T. reports lecture fees from Lilly and Novartis and consultancy fees from Wilmington Healthcare and is author of the book *Life Without Diabetes*. D.T. declares no personal conflict of interest but has permanent employment with Diabetes UK, who has commercial relationships with various pharmaceutical and food companies. No other potential conflicts of interest relevant to this article were reported.

References

1. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ 2020;369:m1361
2. Simmons LR, Molyneaux L, Yue DK, Chua EL. Steroid-induced diabetes: is it just unmasking of type 2 diabetes? ISRN Endocrinol 2012;2012:910905
3. Li Z, Cheng Y, Wang D, et al. Incidence rate of type diabetes mellitus after gestational diabetes mellitus: a systematic review and meta-analysis of 170,139 women. J Diab Res 2020;3076463
4. Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Diabetes 2011;60:298–305
5. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–489
6. Carson AP, Fox CS, McGuire DK, et al. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes 2010;3:661–667
7. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2013;1:28–34
8. Kramer CK, Zinman B, Choi H, Retnakaran R. Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes. BMJ Open Diabetes Res Care 2016;4:e000270
9. McInnes N, Smith A, Otto R, et al. Piloting a remission strategy in type 2 diabetes: results of a randomized controlled trial. J Clin Endocrinol Metab 2017;102:1596–1605
10. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344–355
11. Gregg EW, Chen H, Wagenknecht LE, et al.; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489–2496
12. Mingrone G, Panunzi S, De Gaetano A, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2021;397:293–304
13. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39:861–877
14. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes: 5-year outcomes. N Engl J Med 2017;376:641–651
15. White MG, Shaw JAM, Taylor R. Type 2 diabetes: the pathologic basis of reversible β-cell dysfunction. Diabetes Care 2016;39:2080–2088
16. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care 2009;32:2133–2135
17. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). Br J Diabetes 2019;19:73–76
18. Barnes E. Between remission and cure: patients, practitioners and the transformation of leukaemia in the late twentieth century. Chronic Illn 2007;3:253–264
19. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. Cell Metab 2018;28:547–556.e3

20. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506–2514
21. Camastra S, Manco M, Mari A, et al. Beta-cell function in severely obese type 2 diabetic patients: long-term effects of bariatric surgery. Diabetes Care 2007;30:1002–1004
22. Consensus Committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care 2007;30:2399–2400
23. Jeppsson J-O, Kobold U, Barr J, et al.; International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002;40:78–89
24. EurA1c Trial Group. EurA1c: the European HbA1c trial to investigate the performance of HbA1c assays in 2166 laboratories across 17 countries and 24 manufacturers by use of the IFCC model for quality targets. Clin Chem 2018; 64:1183–1192
25. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
26. Bergenstal RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. Diabetes Care 2018;41:2275–2280
27. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. Diabetes Care 2017;40:994–999
28. Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy non-diabetic participants: a multicenter prospective study. J Clin Endocrinol Metab 2019;104: 4356–4364
29. Hundal RS, Inzucchi SE, Metformin: new understandings, new uses. Drugs 2003;63:1879–1894
30. Herman WH, Ratner RE. Metformin should be used to treat prediabetes in selected individuals. Diabetes Care 2020;43:1988–1990
31. Davidson MB. Metformin should not be used to treat prediabetes. Diabetes Care 2020; 43:1983–1987
32. Yki-Järvinen H. Glucose toxicity. Endocr Rev 1992;13:415–431
33. Isaman DJ, Rothberg AE, Herman WH. Reconciliation of type 2 diabetes remission rates in studies of Roux-en-Y gastric bypass. Diabetes Care 2016;39:2247–2253
34. Ceriello A. The emerging challenge in diabetes: the "metabolic memory." Vascul Pharmacol 2012; 57:133–138
35. Murphy R, Jiang Y, Booth M, et al. Progression of diabetic retinopathy after bariatric surgery. Diabet Med 2015;32:1212–1220
36. Arun CS, Pandit R, Taylor R. Long-term pro-gression of retinopathy after initiation of insulin therapy in Type 2 diabetes: an observational study. Diabetologia 2004;47: 1380–1384
37. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–886
38. Singh RP, Gans R, Kashyap SR, et al. Effect of bariatric surgery versus intensive medical management on diabetic ophthalmic outcomes. Diabetes Care 2015;38:e32–e33