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CONSENSUS REPORT

Consensus report: definition and interpretation of remission in type 2 diabetes

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Abstract

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 vs 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} <48 mmol/mol (6.5%) 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.

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A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel and represents the panel's collective analysis, evaluation and opinion. The article was reviewed for EASD by its Committee on Clinical Affairs.

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Abbreviations

CGM	Continuous glucose monitoring
eA1C	Estimated HbA_{1c}
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide 1
GMI	Glucose management indicator
T2D	Type 2 diabetes

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 hyperglycaemia 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 hyperglycaemia 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, hyperglycaemia 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 hyperglycaemia, sometimes called 'stress hyperglycaemia,' 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 unexpected decline of weight in T2D may allow or require cessation of glucose-lowering treatment.

These changing patterns of glycaemia 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 hyperglycaemia 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 HbA_{1c}. This pattern might be attributed to overtreatment of T2D, leading to an increased risk of hypoglycaemia [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 pharmacological therapy at the time of first presentation of T2D in adults can sometimes restore nearly normal glycaemic control, allowing therapy to be withdrawn [7–9]. Reversal of 'glucose toxicity' accompanying restoration of glycaemic 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 glycaemic control with little tendency to cause hypoglycaemia. Significant behavioural changes—mainly related to nutrition and weight management—can lead to a return from overt hyperglycaemia 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 glycaemic 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 re-evaluation of terminology and definitions that may guide current discussions and future research in managing such transitions in glycaemia 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 hyperglycaemia 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 $HbA_{1c} < 48$ mmol/mol (<6.5%) and/or fasting plasma glucose (FPG) 5.6–6.9 mmol/l (100–125 mg/dl) were used to define a partial

remission, while 'normal' levels of HbA_{1c} and FPG (<5.6 mmol/l [100 mg/dl]) 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 favour specific interventions. Instead, based on consensus reached by the authors, it proposes suitable definitions of terms and ways to assess glycaemic 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 favourable 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 hyperglycaemia 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 hyperglycaemia, 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 the underlying pathophysiology of T2D, including both deficiency of insulin and resistance to insulin's actions, as well as other abnormalities, is rarely completely normalised by interventions [19–21]. In addition, any criterion for identifying a remission of diabetes will necessarily be arbitrary, a point on a continuum of glycaemic levels. Although the previous consensus statement suggested dividing diabetes remission into partial and complete categories, using different glycaemic 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 glycaemic 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 normalised and that no clinical follow-up or further management will be needed either for a recurrence of hyperglycaemia 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.

Glycaemic criteria for diagnosing remission of T2D

Measures widely used for diagnosis or glycaemic 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 favoured HbA_{1c} below the level currently used for initial diagnosis of diabetes, 48 mmol/mol (6.5%), and remaining at that level for at least 3 months without continuation of the usual antihyperglycaemic agents as the main defining measurement. Methods used to measure HbA_{1c} must have stringent quality assurance in place and assays must be standardised to criteria aligned to international reference values [22–24].

However, a number of factors can affect HbA_{1c} measurements, including a variant haemoglobin, 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 haemoglobins 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 haemoglobin 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 7.0 mmol/l (126 mg/dl) can in some settings be used as an alternative 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 glycaemic response to oral glucose, with early hyperglycaemia followed by later hypoglycaemia after an oral glucose challenge, further confounding interpretation of the test.

Considering all alternatives, the group strongly favoured use of $HbA_{1c} < 48$ mmol/mol (<6.5%) 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 glycaemic 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 antihyperglycaemic 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 ovary syndrome [29]. GLP-1 receptor agonists might be favoured 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 glycaemic 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 recognised 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 hyperglycaemia 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 antihyperglycaemic therapy, especially with metformin? This is a controversial area, with arguments both for and against. In favour 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 hyperglycaemia [30]. On the other side is the argument that protection against beta cell deterioration by pharmacotherapy has yet to be convincingly proven and preventive intervention has known costs and potential risks [31].

Table 1 Interventions and temporal factors in determining remission of T2D

Intervention[a]	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	

[a] Documentation of remission should include a measurement of HbA_{1c} just prior to intervention

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 stabilisation 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 stabilises. 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 stabilise at a shorter time after initiation of an intervention, or increase more rapidly if glycaemic 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.

Physiological 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 favourably 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 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 glycaemic patterns may not be sustained indefinitely. Partial regain of weight can occur, and continuing decline of beta 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 hyperglycaemia frequently recurs. Weight gain, stress from other forms of illness, and continuing decline of beta cell function can all lead to recurrence of T2D. Testing of HbA_{1c} or another measure of glycaemic 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 hyperglycaemia, 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 hyperglycaemia 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 hyperglycaemia. In particular, when poor glycaemic 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 glycaemic 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 48 mmol/mol HbA_{1c} (6.5%) as the cut point for diagnosis of remission, as opposed to 42 mmol/mol HbA_{1c} (6.0%), 39 mmol/mol HbA_{1c} (5.7%), 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 glycaemic remission should be further explored. Use of CGM-derived average glucose judged equivalent to HbA_{1c} < 48 mmol/mol (<6.5%) or use of FPG <7.0 mmol/l (<126 mg/dl) instead of HbA_{1c} could be studied.

Validation of the timing of glycaemic 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 glycaemic 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 glycaemic indications may delay recurrence of hyperglycaemia and/or protect against progression of other metabolic disturbances. Objective information on this point is limited, and more research is clearly required.

Evaluation of nonglycaemic measures during remission Improved glycaemic 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—glycaemic remission and could be evaluated. The role of changes in GLP-1 and other peptide mediators after pharmacological, behavioural 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 healthcare professionals and patients Development and standardisation 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 <48 mmol/mol (<6.5%)* 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 glycaemic control, *FPG < 7.0 mmol/l (<126 mg/dl)* or *eA1C < 6.5%* calculated from CGM values can be used as alternative 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.

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