

How Do We Define Cure of Diabetes?

JOHN B. BUSE, MD, PHD¹
SONIA CAPRIO, MD²
WILLIAM T. CEFALU, MD³
ANTONIO CERIELLO, MD⁴
STEFANO DEL PRATO, MD⁵
SILVIO E. INZUCCHI, MD⁶

SUE McLAUGHLIN, BS, RD, CDE, CPT⁷
GORDON L. PHILLIPS II, MD⁸
R. PAUL ROBERTSON, MD⁹
FRANCESCO RUBINO, MD¹⁰
RICHARD KAHN, PHD¹¹
M. SUE KIRKMAN, MD¹¹

The mission of the American Diabetes Association is “to prevent and cure diabetes and to improve the lives of all people affected by diabetes.” Increasingly, scientific and medical articles (1) and commentaries (2) about diabetes interventions use the terms “remission” and “cure” as possible outcomes. Several approved or experimental treatments for type 1 and type 2 diabetes (e.g., pancreas or islet transplants, immunomodulation, bariatric/metabolic surgery) are of curative intent or have been portrayed in the media as a possible cure. However, defining remission or cure of diabetes is not as straightforward as it may seem. Unlike “dichotomous” diseases such as many malignancies, diabetes is defined by hyperglycemia, which exists on a continuum and may be impacted over a short time frame by everyday treatment or events (medications, diet, activity, intercurrent illness). The distinction between successful treatment and cure is blurred in the case of diabetes. Presumably improved or normalized glycemia must be part of the definition of remission or cure. Glycemic measures below diagnostic cut points for diabetes can occur with ongoing medications (e.g., antihyperglycemic drugs, immunosuppressive medications after a transplant), major efforts at lifestyle change, a history of bariatric/metabolic surgery, or ongoing procedures (such as repeated replacements of endoluminal de-

VICES). Do we use the terms remission or cure for all patients with normal glycemic measures, regardless of how this is achieved?

A consensus group comprised of experts in pediatric and adult endocrinology, diabetes education, transplantation, metabolism, bariatric/metabolic surgery, and (for another perspective) hematology-oncology met in June 2009 to discuss these issues. The group considered a wide variety of questions, including whether it is ever accurate to say that a chronic illness is cured; what the definitions of management, remission, or cure might be; whether goals of managing comorbid conditions revert to those of patients without diabetes if someone is “cured”; and whether screening for diabetes complications needs to continue in the “cured” patient. Since little or no scientific or actuarial evidence exists to inform the group’s discussions, consensus was difficult to attain in a number of areas. The opinions and recommendations expressed herein are those of the authors and not the official position of the American Diabetes Association.

Medically, cure may be defined as restoration to good health, while remission is defined as abatement or disappearance of the signs and symptoms of a disease (3). Implicit in the latter is the possibility of recurrence of the disease. Many clinicians consider true cure to be limited to acute

diseases. Infectious diseases could be seen as a model: acute bacterial pneumonia can be cured with antibiotics, but HIV infection, currently, can at best be stated to be in remission or converted to a chronic disease. The consensus group considered the history of childhood acute lymphoblastic leukemia, which evolved from a uniformly fatal disease to one that could be put into remission to one that can now often be considered cured (4). Conversely, chronic myelocytic leukemia is now considered to be in prolonged remission, but not cured, with therapies such as imatinib.

For a chronic illness such as diabetes, it may be more accurate to use the term remission than cure. Current or potential future therapies for type 1 or type 2 diabetes will likely always leave patients at risk for relapse, given underlying pathophysiologic abnormalities and/or genetic predisposition. However, terminology such as “prolonged remission” is probably less satisfactory to patients than use of the more hopeful and definitive term “cure” after some period of time has elapsed. Additionally, if cure means remission that lasts for a lifetime, then by definition a patient could never be considered cured while still alive. Hence, it may make sense operationally to consider prolonged remission of diabetes essentially equivalent to cure. This is analogous to certain cancers, where cure is defined as complete remission of sufficient duration that the future risk of recurrence is felt to be very low.

Abnormal glucose metabolism leading to hyperglycemia defines the disease diabetes, yet hyperglycemia exists on a continuum and the diagnosis of the disease occurs at levels sufficiently high to be associated with the diabetes-specific complication retinopathy. Should absence of the disease diabetes be defined as glucose values considered within the normal range, sub-diabetic but not necessarily normal glucose values, or the complete absence of underlying abnormal physiology such as insulin resistance or β -cell dysfunction or loss?

The group modeled its consensus definitions somewhat on terminology that exists for certain malignancies, with hyperglycemia analogous to tumor load. Cancer may initially be put into remission, either partial (substantial reduction in tumor load) or complete (no evidence of tumor). Eventually, the duration of a

From the ¹Division of Endocrinology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; the ²Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; ³Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana; the ⁴University of Warwick, Warwick Medical School, Coventry, U.K.; the ⁵Department of Endocrinology & Metabolism, Section of Metabolic Diseases and Diabetes, University of Pisa, Pisa, Italy; the ⁶Section of Endocrinology, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut; ⁷Nebraska Medical Center, Omaha, Nebraska; the ⁸Division of Hematology/Oncology, Department of Medicine, and the Wilmot Cancer Center, University of Rochester School of Medicine, Rochester, New York; ⁹Pacific Northwest Diabetes Research Institute and University of Washington, Seattle, Washington; the ¹⁰Section of Metabolic Surgery, Department of Surgery, Weill Cornell Medical College-New York Presbyterian Hospital, New York, New York; and the ¹¹American Diabetes Association, Alexandria, Virginia.

Corresponding author: M. Sue Kirkman, skirkman@diabetes.org.

DOI: 10.2337/dc09-9036

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

complete remission is felt to be sufficient such that the risk of recurrence is likely to be low, and such a prolonged remission might operationally be considered a cure. However, unlike tumor size in people with cancer, glucose levels in people with diabetes may fluctuate greatly from day to day. In a patient with type 2 diabetes, for example, improved or normal glycemia that occurs after only a few days of a stringent diet should certainly not be considered remission. Otherwise, patients could be in and out of remission constantly. The minimum duration of improved or normal glycemia that must occur before being labeled remission was the subject of great debate, and in the end the group consensus was to be conservative. Additionally, although glycemic measures just below the diabetic cut points could be defined as absence of the disease diabetes, the group considered impaired glucose homeostasis a sign of minimal residual disease and hence only a partial remission. The group was unable to reach a consensus on the incremental value of oral glucose tolerance testing, beyond the more convenient A1C and FPG tests, in defining remission.

The authors agreed upon the following definitions, which are the same for type 1 and type 2 diabetes: Remission is defined as achieving glycemia below the diabetic range in the absence of active pharmacologic (anti-hyperglycemic medications, immunosuppressive medications) or surgical (ongoing procedures such as repeated replacements of endoluminal devices) therapy. A remission can be characterized as partial or complete.

Partial remission is sub-diabetic hyperglycemia (A1C not diagnostic of diabetes [$<6.5\%$], fasting glucose 100–125 mg/dl [5.6–6.9 mmol/l]) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures.

Complete remission is a return to "normal" measures of glucose metabolism (A1C in the normal range, fasting glucose <100 mg/dl [5.6 mmol/l]) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures.

Remission of type 2 diabetes could be attained, for example, after bariatric/metabolic surgery or with lifestyle efforts such as weight loss and exercise. Nondiabetic glycemia resulting from ongoing medications or repeated procedures (such as in the dynamic phase of band adjustment after laparoscopic gastric banding) would not meet the definition of remission, as these interventions are con-

Table 1—Summary of consensus definitions and recommendations

Definitions	
Partial remission	Hyperglycemia below diagnostic thresholds for diabetes At least 1 year's duration No active pharmacologic therapy or ongoing procedures
Complete remission	Normal glycemic measures At least 1 year's duration No active pharmacologic therapy or ongoing procedures
Prolonged remission	Complete remission of at least 5 years' duration
Recommendations	
Treatment goals for comorbid conditions	Same as those for patients with diabetes for patients with partial or complete remission of less than 5 years' duration With prolonged remission, could consider goals appropriate for patients without diabetes, as long as there is no recurrence of diabetes and no cardiovascular disease
Screening for microvascular complications	Same protocols as those for patients with diabetes for patients with partial or complete remission of less than 5 years' duration With prolonged remission, could consider screening at reduced frequency depending on the status of each complication With prolonged remission, only consider stopping screening for a particular complication completely if there is no history of that complication

sidered treatment. Remission can be considered an outcome of devices (e.g., gastric banding, endoluminal devices) only after the patient has achieved a steady state and no longer requires repeated adjustments and/or replacements of the device. For type 1 diabetes, remission could potentially be attained after immune modulating or islet-replacement therapies that do not require ongoing immunosuppression but not with transplants that require ongoing immunosuppression or future therapies such as an implanted artificial pancreas.

Prolonged remission is complete remission that lasts for more than 5 years and might operationally be considered a cure. The 5-year period was chosen arbitrarily, since there are no actuarial data indicating the likelihood of relapse over various periods of time from the onset of normoglycemia. It is recognized that the risk of relapse likely remains higher for people with diabetes in remission than for age-, sex-, BMI-, and ethnicity-matched individuals who have never had diabetes.

In addition to hyperglycemia, diabetes is characterized by specific (microvascular) or nonspecific (cardiovascular) complications. Diabetes management includes treating cardiovascular risk factors, such as hypertension and dyslipidemia, often to more stringent goals than those for patients who do not have diabetes. People with diabetes also need regular

screenings for the microvascular complications of the disease, such as retinopathy and nephropathy. If a patient is in remission from diabetes, do they still require diabetes-specific treatment goals and screening protocols, and if so, for how long? The consensus group considered both issues to be a function of risk over time. For cardiovascular disease, the very high risk that diabetes imparts is unlikely to be modified quickly, if ever, by amelioration of hyperglycemia, particularly if the usual coexisting risk factors are still present. For diabetes-specific complications such as retinopathy, risk for incident complications is likely to decline significantly with prolonged normoglycemia, while established complications would likely need ongoing monitoring indefinitely.

In a partial or complete remission of less than 5 years' duration, the goals for treatment of comorbidities (hypertension, dyslipidemia) should remain the same as for those with diabetes (e.g., blood pressure goal $<130/80$ mmHg). When complete remission exceeds 5 years, goals appropriate for a patient without diabetes could be considered, as long as the patient remained without recurrence of diabetes and without cardiovascular events.

In a partial or complete remission of less than 5 years' duration, the patient

should receive screening for the complications of diabetes at the same frequency as when diabetes was present. Once a complete remission exceeds 5 years, complication screening might occur at a reduced frequency (depending on the status of each complication). Completely stopping screening for a particular complication should be considered only if there is no history of that complication.

These definitions and consensus recommendations, summarized in Table 1, are based on what the consensus group felt to be reasonable given the therapies of today. The authors hope that this article

will engender active discussion in the field. As new therapies of curative intent emerge for type 1 and type 2 diabetes and actuarial and scientific evidence regarding prognosis builds, these issues will surely require further deliberation.

Acknowledgments— F.R. is a consultant for Covidien and Ethicon, is on speaker bureaus for NGM Biotech and GI Dynamics, and receives research grant support from Roche and Covidien. The group acknowledges the presence of inevitable potential intellectual conflicts of interest related to their scientific and medical interests. No other potential conflicts of interest relevant to this article were reported.

References

1. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316–323
2. Saudek CD. Can diabetes be cured? Potential biological and mechanical approaches. *JAMA* 2009;301:1588–1590
3. Medial terminology [website]. Available at www.medicalterms.com. Accessed 5 August 2009
4. Barnes E. Between remission and cure: patients, practitioners and the transformation of leukaemia in the late twentieth century. *Chronic Illness* 2007;3:253–264