



Remission of Type 2 Diabetes: A Position Statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS)

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Key messages

- There is ample evidence to support the statement that it is possible to achieve remission in type 2 diabetes.
- Defining remission of type 2 diabetes has not as yet achieved national or international consensus among various organisations and there is no single internationally acceptable definition.
- ABCD and PCDS recognise the importance of a consensus definition, which has significant implications for people who achieve remission of type 2 diabetes, as well as health services.
- We propose in this position statement a practical definition of remission of type 2 diabetes and call upon other societies to come together to work with us to agree an internationally agreed definition. This will allow an international platform for further research and data collection.
- In responsive individuals, where type 2 diabetes is associated with weight gain or obesity, remission in type 2 Diabetes can be achieved through several means and all require a sustainable weight loss. This is particularly true in the early stages of type 2 Diabetes when irreversible damage to the beta cell has not happened.
- Once achieved, remission must be sustained to gain the full health benefits.
- Of the various strategies shown to be effective, weight loss through bariatric surgery or low calorie diet, remain the most successful methods. Both require ongoing sustained modest restriction of energy intake and increase in daily physical activity.
- We acknowledge that weight loss achieved by any means, including unintentional weight loss, may contribute to remission of type 2 diabetes.
- Implicit in defining remission is that biochemical parameters must have been achieved and maintained following the discontinuation of all glucose-lowering therapies.
- We acknowledge that there is considerable debate in the scientific community about the duration over which HbA1c or fasting plasma glucose levels must be maintained to define remission. However, we have adopted a pragmatic approach, believing 6 months to be a reasonable duration, aimed at encouraging motivation and sustained weight loss to achieve remission over a longer period.
- Consistent coding for remission of diabetes is required to facilitate safe follow-up and data collection in routine clinical practice.

ABCD and PCDS strongly recommend that “diabetes resolved” clinical codes should not be employed in clinical practice but that “diabetes in remission” codes should preferentially be adopted.

- Finally, it is important, that in those individuals who achieve and sustain remission, robust systems are in place to call and recall these individuals for annual review and that primary care is adequately resourced to facilitate this.

Introduction:

It has been recognised for some time that type 2 diabetes can be reversed and remission of type 2 diabetes can be achieved. The first evidence of this came from studies of bariatric surgery in individuals with type 2 diabetes (1, 2). Even before then there was evidence that the hyperglycaemia and its associated pathophysiological disturbances can be reversed by adopting a hunter gatherer style and within a short period of time (3, 4). There were sufficient studies showing that by changing life style dramatically the control of diabetes can be significantly improved and a significant proportion of patients can either reduce or come off their glucose-lowering therapies (5-7).

More recent studies have provided further proof of concept that type 2 diabetes can be reversed but importantly have demonstrated the underlying mechanism i.e. a reduction in the fat content of liver and pancreas, dependent upon beta cell capacity for recovery (8-10). Where beta cell failure has already occurred, weight loss is unlikely to be successful in reversing diabetes.

Once achieved, remission appears durable provided weight regain does not occur. This has been formally demonstrated in DiRECT, with clear evidence of gradual continuing improvement in beta cell functional capacity over at least 12 months (10). The old idea that beta cell function inevitably declines over time in people who have developed type 2 diabetes has been definitively disproven. Metabolic control has been shown to be maintained over several years if remission is first achieved (11-13). The study of Lim et al (8) was first presented to the 2010 meeting of the Association of British Clinical Diabetologists (ABCD), reporting the index case of diet-induced remission of type 2 diabetes - now known to have remained normoglycaemic 14 years after stopping glucose-lowering therapies. Describing such people as not having diabetes is important not only for insurance purposes but also as a motivating factor to avoid weight regain. The term 'post-diabetes', has been suggested to describe the state after weight-loss induced remission of type 2 diabetes. This retains the implication that there is susceptibility to return diabetes if weight regain occurs, whilst indicating that the major cardiovascular risks associated with pre-diabetes are not present - even if plasma glucose might usually remain in the range associated with the high-risk state of pre-diabetes (14). In UK Primary Care, the Read code would appropriately be assigned, indicating remission of diabetes but continuing need for annual checks (15).

However, defining cure or remission of type 2 diabetes has not achieved consensus among international societies. In 2009, the American Diabetes Association (ADA) produced a commentary and statement by an expert group which concluded with summary of consensus achieved by this

group and recommendations to define partial remission and full remission (16). Subsequently, Diabetes UK published a brief interim position statement and concluded that it was not possible to achieve consensus and they-planned further work.

This position statement by the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS) was commissioned after discussions with DUK and agreement with ABCD and PCDS committee members. It is our understanding that further work is planned in the foreseeable future. ABCD and PCDS have therefore taken a pragmatic approach and looked at the available research to date and produced this position statement. The views in this paper are those of authors and endorsed by members of the ABCD and PCDS committees.

In strict medical terms, cure can be defined as restoration of health and no evidence of the disease process as evidenced by whatever available criteria to diagnose the disease or condition in question. However, medical remission is defined as absence of signs and symptoms of the disease (thyrotoxicosis due to Grave's disease is a good example). Therefore, it is implied that disease can recur at any time in the future. This is particularly true of type 2 diabetes

Type 2 diabetes has been regarded as a chronic condition and in this context, remission would appear to be a favourable term while considering the risk of future relapse. The central and important argument is: should the remission of diabetes be defined as return to normal glucose tolerance or at levels of glycaemia which may not be normal, but when the risk of chronic micro- and macro-vascular complications is low or absent.

Why is it important to define remission of Type 2 Diabetes?

The prime importance of defining remission is the motivation this provides to individuals in striving for freedom of diabetes. Many people with type 2 diabetes want to be certain of removing the social stigma they feel with the label 'diabetes', of decreasing the number of tablets to be taken, of removing the threat of complications, decreasing the time spent in doctors' waiting rooms and avoiding the excess costs applied to holiday and life insurance. A further major reason for defining remission is to allow gathering of objective information from medical records for monitoring purposes. There are potentially substantial gains in resources for Society and the health economy in general, by spending less on medication, monitoring, and long term complications. Any resources

thus freed up can be used elsewhere to improve health. Therefore, agreeing a definition of remission may have huge implications.

There are two important considerations underlying a definition of remission:

(a) The glycaemic threshold at which remission can be said to have been achieved: should this be at HbA1c < 48 mmol/mol, fasting glucose < 7.0 mmol (the internationally agreed diagnostic threshold for type 2 diabetes), or at HbA1c < 42 mmol/mol, fasting glucose <6.1 mmol, which defines normalcy according to current diagnostic criteria;

(b) The duration over which any given level of glycaemia should be maintained before remission can be diagnosed. This second point perhaps being more difficult to agree.

ADA has previously proposed (16) the terms:

Partial remission: i.e. return of glycaemia below diagnostic threshold for type 2 diabetes for at least one year.

Complete remission, where're glucose tolerance is normal at least for one year

In both scenarios, these thresholds must be achieved without need for pharmacological treatments.

Furthermore, prolonged remission was defined as remission of at least 5-years duration.

ABCD and PCDS are of the view that defining remission in this way has some drawbacks. It is complicated (with 2 definitions, rather than one) and would require a complex coding mechanism, with need to draw clear distinction between partial and complete remission. This in itself justifies a single definition.

Therefore, we propose a single definition of remission i.e., achievement of glycaemia below the threshold currently used for diagnosis of Type 2 Diabetes and sustained for a minimum period of 6 months, having discontinued all glucose-lowering therapies. We believe this is a simple and pragmatic definition which will allow a unified application at least in the UK and other health systems.

Recommendation

Remission of type 2 diabetes can be diagnosed when a person with confirmed type 2 diabetes has achieved all three of the following criteria: (i) Weight loss; (ii) Fasting plasma glucose or HbA1c below the WHO diagnostic threshold (<7mmol/l or <48mmol/mol, respectively) on two occasions separated by at least 6 months; (iii) the attainment of these glycaemic parameters following the complete cessation of all glucose-lowering therapies.

This opinion has been based upon sound information. Development or progression of microvascular complications is unlikely below the threshold for diagnosing diabetes, and indeed this was a major part of the original ADA and WHO reasoning to adopt this diagnostic criterion (17). Macrovascular risk is sharply decreased by weight loss, as indicated by 10 year cardiovascular risk (QRISK) decreasing from 23% to 7% after 6 months steady weight following diet-induced remission of type 2 diabetes (9, 18). This remarkable health gain is explained by the improvement in lipid status as well as mean blood pressure and weight (9). Both microvascular and macrovascular risk has been shown to decrease sharply after bariatric surgery induced remission, and microvascular complications regress after pancreas transplantation (19, 20).

Does this proposed definition have implications for health care system? Of course, it does. All individuals who achieve remission defined as we propose should and must continue with regular surveillance and management of other risk factors as previously agreed for blood pressure and lipid management and also annual screening for complications. However, evidence gathered in future may help identify individuals who are likely to remain in prolonged remission and those who are likely to relapse. Emerging evidence suggest that the achievement and sustainability of remission is dependent upon the capacity of beta cell to recover its insulin secretion (10).

Further care of those who achieve remission:

It is important to recognise that continued support from healthcare professionals is required to maximise the likelihood of long-term avoidance of weight regain (20, 21), and hence the need for regular review once remission is achieved. DiRECT has been followed by a programme of 3-monthly appointments, and the success of this will be assessed in due course. Weight regain in the first year was observed to be predominantly early, with only modest regain thereafter (22).

Evidence based Interventions that are effective in achieving remission:

What are the current evidence based interventions available to achieve and maintain remission of type 2 diabetes?

(1) Bariatric surgery

(2) The introduction of short term major caloric reduction, with total diet replacement and a stepped food re-introduction

It is clear that significant weight loss is a pre-requisite to achieving remission of type 2 diabetes, but shorter duration of diabetes is also an important factor associated with successful recovery of residual beta cell function.

The DiRECT trial showed that application of dietary modifications aimed at achieving a 12-month remission was a real possibility (23).

Implications for patients with Type 2 Diabetes:

Clear cut criteria to define remission will remove any doubt as to a person's diabetes status for insurance purposes. After undergoing major dietary restriction, it is demotivating to be told that diabetes is still present even though HbA1c is below the diagnostic threshold. Conversely, identification of a threshold focusses the need to avoid weight regain. In addition, we believe that a significant lowering of cardiovascular risk associated with remission must be an additional motivating factor for individuals to sustain remission.

Implications for coding and service provision for those who achieve remission:

Currently, clinical coding for diabetes remission is not widely acknowledged or used. Clear cut information on the numbers of people who achieve remission of type 2 diabetes, and on the subsequent time course will facilitate health care planning and resource allocation. Therefore, defining remission is of paramount importance.

Further Research:

The ongoing follow up of DiRECT will provide detailed information about remission of type 2 diabetes up to 5 years. Ongoing collation of clinical data, made possible by the clear definition of remission of type 2 diabetes, will be vital to inform future health care and policy decisions.

Summary:

Recent evidence has informed our recommendation regarding the definition of remission of type 2 diabetes. Achievement and maintenance of HbA1c of <48mmol/mol (or fasting plasma glucose <7.0mmol/l) after weight loss and the discontinuation of all glucose-lowering therapies over 6 months or longer, allows a clear, evidence-based definition of diabetes remission. The need for ongoing supportive follow up is implicit in the formal recognition of remission, given the risk of weight regain.

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