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Remission of Type 2 Diabetes Mellitus: Emerging Concepts and Proposed Diagnostic Criteria

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Abstract

The remission of type 2 Diabetes is a topic that has been widely discussed recently and it gives new hope for people with diabetes. Achievement of normal blood glucose levels or levels below the diagnostic threshold for diabetes without pharmacotherapy among people with Type 2 Diabetes after metabolic surgery and carbohydrate or calorie-restricted diet paved the way for more enthusiastic research in this area. There is a lot of confusion regarding the appropriate terminology and definition of remission of diabetes. In this short review, we are briefly analyzing the emerging concepts and proposing criteria for diagnosing remission of diabetes, which will be helpful for healthcare providers and people with diabetes.

INTRODUCTION

The remission of type 2 Diabetes is a topic that is widely discussed not only among healthcare professionals but also among the public^[1]. Present reports of achievement of normal glucose levels without pharmacotherapy among people with Type 2 Diabetes after metabolic surgery and carbohydrate or calorie-restricted diet paved the way to more enthusiastic research in this area. There is a lot of confusion regarding the appropriate terminology. Various professional bodies define remission of diabetes differently, again adding to the confusion among healthcare providers and the public^[2].

Various terminologies

Various terminologies used in this aspect include reversal, resolution, cure and remission,

Diabetes 'resolution' implies that an entirely normal state has been established permanently. 'Cure' of diabetes gives the impression that all the pathophysiological aspect is normalized and further follow-up or management is not required. Diabetes "reversal" indicates the return of blood glucose levels below those used to diagnose diabetes but it doesn't imply that further support is needed to prevent an increase in blood glucose level. Diabetes "remission" indicates returning of blood glucose levels to normal or below the threshold used to diagnose diabetes and the need for continued support^[3-5]. Hence "remission" is the term widely used to denote those who achieved blood glucose levels below those used to diagnose diabetes as they require continued support and regular follow-up to maintain blood sugar value below the threshold level, identify relapse at the earliest if it occurs, and monitor for complications (Table 1).

Remission of diabetes- Pathophysiological basis

In people with Type 2 Diabetes, insulin resistance, hyperinsulinemia, and subsequent hyperglycemia are the predominant pathophysiology in the early stages followed by deterioration of beta cell function and insulinopenia, in the later part of the disease. Any measures reducing insulin resistance like weight reduction will result in improvement in hyperglycemia and even normalization of blood sugar value. Similarly, any measures that improve insulin secretion also improve hyperglycemia in people with diabetes. In addition to that reduction in the insulin requirement also will help to control blood glucose value even at the stage of insulinopenia.

As per the twin cycle hypothesis chronic calorie excess leads to the accumulation of fat in the liver and subsequently in the pancreas^[6] (see Fig 1). Accumulation of fat in the liver leads to hepatic insulin resistance and that in the pancreas leads to impaired

insulin secretion. When fat deposition exceeds the “personal fat threshold” of that person, he develops type 2 diabetes mellitus (DM)^[7].

Based on the twin cycle hypothesis, weight reduction is associated with improvement in fatty infiltration of the liver and pancreas, thereby improving insulin resistance and insulin secretion, which is responsible for remission of diabetes as per the current concepts^[8]. Significant weight loss (about 15kg) is an important factor in predicting the chance of remission.

The remission of diabetes is not just the normalization of glycemic status in the absence of active therapeutic intervention. Improvement in glycemic status is the reflection of improvement in the pathophysiological aspect of Type 2 Diabetes, i.e. improvement in insulin secretion and insulin resistance.

So, the extent and duration of normalization of blood sugar depends upon the extent of improvement of insulin resistance and improvement in insulin secretion. Hence people with Type 2 diabetes who achieved remission require regular monitoring to identify the re-emergence or relapse of diabetes.

Depending upon the extent of normalization of glycemic status remission is divided into two – Partial remission or complete remission^[9] (Fig 1). Depending upon the duration of remission achieved we classify it into transient remission, short-term remission, long-term remission, and prolonged remission. Those without established diabetes, i.e. Pre-diabetes can also achieve normalization of glycemic status and is usually complete remission.

Euglycemia achieved because of continuous carbohydrate restriction, which only lasts as long as carbohydrate restriction is maintained is called ‘state of mitigation’ which has to be differentiated from remission^[10].

In people with diabetes, normalization of blood sugar value can persist for variable periods after temporary use of pharmacotherapy because of improvement in the deleterious effect of poor metabolic control on insulin secretion and action (e.g. glucotoxicity and lipotoxicity) without altering the basic pathophysiology of diabetes. This should not be confused with remission, as there is no improvement in the

pathophysiologic mechanism. Remission of diabetes has to be differentiated from mere normalization of blood glucose levels.

Challenges in the diagnosis of remission

To define remission, people with previously diagnosed Type 2 diabetes should have sustained normal blood glucose values (complete remission) or below the diagnostic threshold for diabetes (partial remission) by any means like blood glucose testing (Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Random Blood Sugar (RBS), Oral Glucose Tolerance Test (OGTT)), glycated hemoglobin (HbA1c), Continuous Glucose Monitoring (CGM) values, eA1c (estimated A1c level) or GMI (Glucose Management Indicator). Each method has its advantages and limitations.

Blood sugar values (e.g. FBS, PPBS, RBS) undergo wide fluctuation and show significant variation between repeated measurements. Similarly, 2-hour Post-Glucose after 75g oral glucose load is also associated with high variability between repeated measurements^[11]. FBS and CGM values are more variable and hence some experts recommend repeated testing to confirm remission. In those with post-bariatric surgery, there is early hyperglycemia followed by later hypoglycemia making interpretation of 2-hour PG value difficult^[5].

HbA1c is an inaccurate indicator of glycemic status in certain conditions like anemia, with abnormalities of RBC survival, those with hemoglobin variants, Splenomegaly, Asplenia, Uremia, Severe hypertriglyceridemia, etc^[12,13].

CGM values can be used to diagnose remission and estimated HbA1c (eA1c) or glucose management indicator (GMI) can be calculated from it and used to establish remission. HbA1c of < 48 mmol/mol (<6.5%) calculated from 24-hour CGM values can be used to denote remission^[5].

Ideally, HbA1c, Fasting Plasma Glucose, 2-hour post-prandial plasma Glucose, CGM, eA1c, and GMI all should be within normal limits or below the level for the diagnosis of diabetes to diagnose remission. However, it is practically very difficult and time-consuming to measure all these parameters to establish remission. There is a subset of

people with diabetes having normal FBS and high 2-hour Post-prandial Glucose and if we measure only FBS in such individuals and diagnose remission, it will be a false diagnosis of remission. A similar situation can happen in people with high fasting and normal 2-hour Plasma Glucose levels. Even though it is not practical to do all these measurements, it is always better to select the test that has the maximum chance to detect any blood sugar value above the cut-off in that particular patient. If there is any probability of getting a false value with any of the above methods, another alternative modality has to be used to confirm remission.

While selecting a particular test to demonstrate normoglycemia, one should consider the inherent property of the test, like the duration of the glycemic status that particular test represents (Fig 2). For example, HbA1c reflects the glycemic status of the last 3-4 months. So if we do HbA1c before 3 months of stopping of anti-diabetic treatment, we will get a false low HbA1c, indicating 'remission' even when it is actually not present. So HbA1C has to be done after a minimum of 3 months after the washout period of a particular intervention.

Similarly, tests to assess normoglycemia, should not be performed before completing the washout period of a pharmacotherapy or intervention (Fig 2). For almost complete elimination of any medication, it usually takes 4 to 5 half-life ($t^{1/2}$). For example, the $t^{1/2}$ of metformin is 17.6 h, and usually, it will take 5 $t^{1/2}$ ($5 \times 17.6 \text{ h} = 98.6 \text{ h}$) for the medicine to almost completely eliminate from the body^[14]. So FBS, PPBS, and CGM should not be done to demonstrate normoglycemia after stopping therapy before 98.6 h in people who stopped metformin recently.

Once remission is achieved, it is difficult to predict how long it will persist. But there are a lot of factors like duration of diabetes, body weight, β -cell function, *etc.* which help to assess the feasibility of remission. The duration of remission is a retrospective assessment. Those who maintain 5 years of remission are said to have achieved "prolonged remission"^[9].

The durability of remission varies with the interventions and bariatric surgery usually gives long-lasting remission compared to other modalities^[15]. So it is better to

mention the intervention adopted to achieve remission than simply mentioning “remission of diabetes”. E.g., “remission of diabetes achieved by bariatric surgery”.

Diet control and exercise are integral parts of treatment of diabetes. Hence it is called non-pharmacological therapy, medical nutrition therapy, *etc.* Another important concern while defining criteria for remission of diabetes is whether one can continue non-pharmacological therapy like dietary intervention and exercise or not.

In an ideal condition, remission of diabetes requires persistent normalization of blood sugar values even after withdrawal of all the interventions (pharmacological and non-pharmacological), so that its direct blood sugar-lowering action will be washed out. However, all the current definitions do not require the withdrawal of non-pharmacological interventions like diet control and exercise to define remission^[1,2]. In our opinion, it is better to add “maintained with diet control and or exercise” to the diagnosis of diabetes remission to understand the ongoing interventions and to emphasize the need for continuing diet control and exercise to maintain remission.

Another important concern is about the withdrawal of interventions or pharmacotherapy. Some guideline says that the patient should be off all anti-diabetic medication, while others say it is ok to continue medication like metformin if it was started for non-glycemic indication (i.e., for other than blood sugar control)^[1,2]. Examples of such medications, started for non-glycemic indication which have beneficial effects on blood sugar value, include liraglutide for obesity, SGLT 2 Inhibitors for heart failure and renal protection, and metformin for PCOD.

Even if the drugs that reduce blood sugar are started for non-glycemic indications like metformin in PCOD, GLP-1 against for weight loss and cardiovascular benefit, and SGLT-2 inhibitor for heart failure or renal protection it is not advisable to stop these drugs just to confirm ‘remission’, increasing the risk of complications of the underlying problem for which the medication was started. But for those who are on these medications, even if the blood glucose parameters are within normal limits, we cannot ideally consider it as “remission” and is better categorized as “incomplete remission”.

The effect of Pharmacotherapy or Bariatric surgery is evident fast, but lifestyle intervention is slow (requires more time) and it may require up to 6 months to stabilize the effect^[5]. And again 3 months period is required for the HbA1c to reflect these changes^[5]. Follow-up HbA1c monitoring should not be done more frequently than every 3 months and not less than every year. Compared to HbA1c, FBS or eA1c derived from CGM stabilizes early and can be used to monitor early. However, as these values are more variable, it should be confirmed by repeated measurement.

Even though as per the current concepts we need a 3-month period to diagnose remission, tests that reflect glycemic control early can be used to document remission after the washout period of pharmacotherapy/intervention, even before completing 3-month period.

Follow-up after remission

For those with poorly controlled diabetes, rapid reduction in blood sugar, and HbA1c may result in worsening of microvascular complications like retinopathy^[5]. Hence rapid reduction of HbA1c in people with retinal changes beyond microaneurysms (more than background retinopathy) is not advised.

Weight gain, stress, poor sleep, and inability to maintain a healthy lifestyle and diet may result in relapse of diabetes in those who already achieved remission. Metabolic memory-like phenomena can occur even after remission, resulting in the development of classical complications of diabetes after remission. So those who achieved remission need regular medical supervision not only to monitor glycemic status but also complications like retinopathy, neuropathy, nephropathy, and cardiovascular complications^[5,16]. In those with poorly controlled diabetes achieving rapid normalization of glycemic status, diabetic retinopathy can worsen (beyond microaneurysms). However, this risk is less after metabolic surgery^[17].

Proposed diagnostic criteria

Our diagnostic criteria contain five components and all five components should be satisfied to make a diagnosis of “remission of type 2 diabetes” (Table 2).

1. Establishing the diagnosis of type 2 diabetes mellitus/ pre-diabetes

As per the criteria, a clear diagnosis of type 2 DM is a prerequisite for the diagnosis of remission. Any transient hyperglycemia misdiagnosed as type 2 DM results in an erroneous diagnosis of remission.

2. Evidence of maintenance of normal blood sugar or blood sugar below the threshold for diabetes (biochemical remission) in people with established diabetes in the absence of any active intervention

Demonstration of normal glycemic parameters or blood sugar below the threshold for diabetes is an essential component of the diagnosis of remission. Various parameters like FBS, PPBS, HbA1c, eA1c, CGM, GMI, *etc.* can be used to document remission. All these tests are associated with their own merits and limitations. So, if there is any chance for a false result of a particular test in one patient (e.g. HbA1c in people with anemia), an alternative test has to be done to demonstrate remission. A single type of test (e.g. PPBS) may not reflect glycemic status in some patients, and in such a situation, multiple types of tests are required. E.g. PPBS may be low in people who underwent metabolic surgery, where FBS or CGM may sometimes pick up abnormal blood sugar values.

3. Duration criteria- for the intervention and for the test

Persistence of normoglycemia even after the withdrawal of glucose-lowering intervention (pharmacotherapy / active intervention) is documented after a reasonable period to wash out the direct effect of medication or intervention. The glucose-lowering intervention can be non-pharmacological (medical nutrition therapy or physical activity) or pharmacological intervention (medication or surgical intervention). There should not be any ongoing pharmacological or surgical procedures (ongoing procedures like repeated placement of endo-luminal devices or intragastric balloons). However non-pharmacological (medical nutrition therapy or physical activity)

interventions are continued in most of the reports of remission. Should non-pharmacological interventions (medical nutrition therapy or physical activity) be discontinued to diagnose remission? Ideally, the answer is “yes”. But for all practical purposes, the answer is “no”. In our opinion in people who achieved remission and continue non-pharmacological interventions, better to mention that “remission is maintained with diet control and or exercise”.

The testing should be scheduled in such a way that the value must reflect the glycemic status after the washout period of the intervention. E.g., HbA1c after 3 months of washout period of intervention. Similarly, the washout period of the intervention also has to be considered while scheduling the test. Usually after pharmacological therapy washout period is after $5 t^{1/2}$ of that particular drug.

Duration of remission; is a retrospective assessment. A minimum of 3 months of maintenance of blood sugar below the specified level is required to categorize it as remission. And remission for more than 5 years is called prolonged remission. We classify remission as transient, short-term, long-term, and prolonged remission if it lasts less than ²6 months, 6 months to 1 year, 1 to 5 years, and more than 5 years respectively.

4. Evidence of improvement of the pathophysiological mechanism

Normalization of blood sugar value as a result of improvement in insulin secretion and insulin resistance helps to differentiate remission from mitigation. Significant weight loss is considered as indirect evidence of loss of fat from the liver and pancreas resulting in improvement in insulin secretion and insulin resistance. So, weight loss is considered as an evidence of improvement of the pathophysiological mechanism.

5. Satisfying exclusion criteria.

Exclusion of transient hyperglycemia and improvement after removal of precipitating event or drugs (E.g. Stress hyperglycemia, drug-induced hyperglycemia) or normalization of blood sugar due to complications (e.g. diabetic kidney disease),

comorbidities or concomitant illness (like malignancy, sepsis, or endocrine disorders) is important to avoid false categorization as ‘remission of type 2 diabetes’.

Interpretation of criteria

In a person with established Type 2 DM, if there is an achievement of glycemic status below the diabetes range (i.e., Pre- Diabetes range) (Partial remission) or within the normal limit (complete remission) and satisfying duration, pathophysiological improvement and exclusion criteria, we can categorize it as ‘remission’ (Table 3). Those not satisfying pathophysiological improvement criteria have to be categorized as “Type II mitigation”. Those satisfying all these criteria but medications that can reduce blood sugar are continued for the non-glycemic indication are categorized as “incomplete remission” (incomplete partial remission if blood sugar is in the pre-diabetes range and incomplete remission if blood sugar is in the normal range).

CONCLUSION

Achievement of normal glucose levels or levels below the threshold for the diagnosis of diabetes without pharmacotherapy among people with Type 2 diabetes after metabolic surgery and carbohydrate or calorie-restricted diet resulted in remission. The twin cycle hypothesis helps to understand the pathophysiological mechanism leading to remission. The lack of clear-cut criteria for diagnosing remission is a biggest challenge healthcare professional are facing now. As per our proposed criteria, 5 components should be satisfied to diagnose ‘remission of type 2 diabetes’. Our proposed criteria will be useful for healthcare professionals worldwide for diagnosing remission.

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