

Cure of Diabetes: Dream or Reality

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INTRODUCTION

Diabetes is a complex, chronic illness requiring continuous medical care with multiple risk reduction strategies beyond glycaemic control. Type 2 diabetes mellitus (T2DM) is now emerging as one of the main threats to human health in the 21st century. By 2025 AD, there will be 300 million people suffering from T2DM globally and India will have the highest number of cases (57.2 million) of all the countries.¹

Similarly, approximately 1.89 per 1,000 children and youth have diabetes. Over 80% of those children under the age of 10 years, and the majority of children between the ages of 10 years and 19 years have Type 1 diabetes mellitus (T1DM). T1DM has been increasing by 3–4% per year in children and youth,² although the incidence seems to be lower in India.

As any other health ailment, we treat diabetes related hyperglycaemia and associated complications. But the question remains that, “Can we actually ‘cure’ diabetes once and for all?” Can we really declare a patient “free” from diabetes or is the concept of diabetes “cure” utopian one?

The website of the American Diabetes Association on its homepage mentions its mission as “...to prevent and **CURE** diabetes and to improve the lives of all people affected by diabetes”. Before we proceed further, we must understand the meaning of certain outcome related terms used during the course of treatment of diabetes.

REMISSION AND CURE

The ADA, in a consensus statement in 2009, mentioned that medically, “**cure**” may be defined as restoration to good health. Many clinicians consider using the term cure to be limited to acute diseases, e.g., acute bacterial pneumonia, which can be “cured” by antibiotics.³

The ADA also mentioned that the term “**remission**”, which means abatement or disappearance of the signs and symptoms of a disease, might be more suited to be used in the context of a chronic illness, e.g., diabetes mellitus.³

Diabetes is defined by the presence of hyperglycaemia, which exists in a continuum, unlike a “dichotomous” disease such as cancer. The hyperglycaemia of diabetes can be impacted over a short period of time by regular treatment or events (medications, diet, activity, and intermittent illness).

Hence not in strict terms, rather for all practical purposes, “**prolonged remission**” of diabetes should be considered to be equivalent to diabetes “**cure**”.³

Similarly, the “Diabetes UK interim position statement on remission in adults with Type 2 Diabetes” mentioned that “the use of the term ‘**remission**’ currently best reflects the situation where someone is relieved of diabetes symptoms and the need for management with blood glucose lowering medications, without down playing the risk of relapse and essential need for ongoing review. There is

Table 1— Summary of consensus definitions and recommendations

Definitions

Partial remission

Hyperglycaemia below diagnostic thresholds for diabetes
At least 1 year's duration
No active pharmacologic therapy or ongoing procedures

Complete remission

Normal glycaemic 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

Source: Reproduced from "Buse JB, Caprio S, Cefalu WT, et al. How Do We Define Cure of Diabetes? Diabetes Care. 2009; 32(11):2133-5".

currently no evidence that this state could be achieved permanently. For this reason Diabetes UK does not support the use of the term 'cure' and any other that suggests a permanent solution".⁴

Attempts to Achieve Remission in Type 2 Diabetes Mellitus

1. Intensive Therapeutic Lifestyle Changes

The most important aspect of T2DM management is "Therapeutic Lifestyle Change".

The "Look Ahead Study",⁵ in 2012, showed that intensive lifestyle intervention comprising of reducing total caloric intake to 1,200–1,800 kcal/day

through reductions in total and saturated fat intake and by increasing physical activity levels to 175 minutes/week resulted in a remission rate of 9.2% at 2 years of follow-up.

"Remission" was defined as transition from meeting diabetes criteria to a pre-diabetes or non-diabetic level of glycaemia (Fasting blood glucose < 126 mg/dL, HbA_{1c} < 6.5%).⁵

The "Predimed Study"⁶ showed that putting newly detected cases of T2DM on "Low Calorie Mediterranean Diet" resulted in a remission rate of 5% at 6 years follow-up.

The "Counterpoint Study"⁷ showed that an "acute negative energy balance" achieved by restricting cases of T2DM to a total energy intake of 600 kcal/day resulted in normalisation of both β -cell function and hepatic insulin sensitivity within 8 weeks.

The "Counter Balance Study"⁸ showed that taking Very Low Calorie Diet (624–700 kcal/day) followed by stepped food reintroduction to isocaloric diet with intensive education and lifestyle modification lead to remission in 40% cases for at least 6 months.

The "DiRECT" study, which was an Open-label, cluster-randomised trial at 49 primary care practices in UK where the persons with BMI of 27–45 kg/m² was selected. 850 kcal diet was allowed for 3 months to 5 months, followed by food re-introduction for 2–8 weeks. Ongoing structured programme continued till 12 months. At the end of 12 months, significantly more people in intervention group experienced weight loss and remission of diabetes.

2. Bariatric Surgery

Although diabetes is traditionally viewed as a chronic, relentless disease in which delay of end organ complications is the major treatment goal, bariatric surgery offers a novel endpoint—major improvement or even complete disease remission.⁹

There are various types of bariatric procedures:

- LAGB (Laparoscopic Adjustable Gastric Banding)
- RYGBP (Roux-en-Y Gastric By Pass)
- BPD (Bilio-Pancreatic Division)
- SG (Sleeve Gastrectomy), etc.

As per a joint statement by the major International Diabetes Organisations in 2016, metabolic surgery should be recommended to treat T2DM in patients with:¹⁰

- BMI ≥ 40 kg/m²
- BMI 35–39.9 kg/m² where hyperglycaemia is inadequately controlled by lifestyle and optimal medical therapy.

For Asian patients,¹⁰ these BMI thresholds should be reduced by 2.5 kg/m².

However, there is no reliable long-term data to view surgery as a permanent cure, though remission upto 15 years has been reported. Taking into account the variability in the remission rates of different surgical procedures, an 8-year diabetes-free interval has been estimated overall. This remission wanes overtime at an estimated rate of 20% over the next 3 years and 25–30% over the next 5 years.¹⁰⁻¹³

3. Early Insulin Therapy

Introducing insulin early, even for a short period of time, during the treatment of T2DM, is a proven, and effective way to revert glucotoxicity and lipotoxicity. There is a very high level of evidence to support the fact that early insulinisation (using MSI or CSII) in a patient with severe symptomatic hyperglycaemia retards β -cell damage and remission rates as high as 42% at 24 months follow-up have been observed.¹⁴

ATTEMPTS TO ACHIEVE REMISSION IN TYPE 1 DIABETES MELLITUS

1. Pancreatic Transplantation

It is a therapeutic option with a potential to induce long-term remission in cases of T1DM.

It is mostly carried out along with a concomitant renal transplantation.

Current 5-year graft survival rates are reported to be upto >83%.

However, the procedure is bedevilled by significant morbidity and mortality.

2. Islet Transplantation

It involves transplantation of pancreatic islets obtained from a deceased donor into the patient's liver.

3. Stem Cell Therapy

This therapy has the potential to cure Type 1 diabetes.

CURE OF SECONDARY DIABETES

Therapeutic “cure” can be achieved in case where diabetes is due to an underlying and treatable secondary cause, e.g., Cushing's syndrome, Acromegaly, and Pheochromocytoma.

High index of suspicion is warranted in patients with uncontrolled diabetes, so as not to miss the diagnosis of a potentially treatable secondary cause.

Removal or substitution (if the patient's condition permits) of offending drugs can also lead to cure of diabetes, e.g., steroid therapy.

HOUSSAY PHENOMENON¹⁵

Because of a new onset pituitary dysfunction (and the subsequent loss of counter-regulatory hormones) a previously diabetic patient can experience increased insulin sensitivity resulting in hypoglycaemia or complete amelioration of diabetes.

Clinicians should be aware of this possibility while encountering hypoglycaemia in previously stable diabetic patients.

Judicious hormone replacement is needed for these patients.

SPONTANEOUS REMISSION OF DIABETES MELLITUS

There have been documented cases where the disease went into remission by itself. There are many theories as to why this could have happened but none have been verified.

SUMMARY

Diabetes is a chronic and multi-systemic disease which has evolved as a pandemic. The theoretical concept of a permanent “cure” seems a far-fetched idea.

However, intensive therapeutic lifestyle changes, coupled with aggressive early insulinisation and bariatric surgery holds promise to prolong remission of the dysglycaemia of T2DM as well keeps the associated complications at bay.

Similarly, pancreatic and islet transplantations

can also induce long-term remission in patients with T1DM.

One must always be on the look-out for an underlying secondary cause of diabetes in a patient with uncontrolled diabetes.

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