METABOLIC U-TURN: TYPE 2 DIABETES MELLITUS REMISSION AND THE IMPLICATIONS OF A TURN IN THE RIGHT DIRECTION

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Executive Summary *Type 2 diabetes mellitus (T2DM) remission is increasingly being acknowledged clinically, as well as in the literature, challenging the paradigm that T2DM is an inevitably progressive disease. Does this signal an opportunity to escape a major public health tra ſc jam with certain collision, as the burden of disease from diabetes rises to epidemic proportions across the globe? An increase which continues, despite recent advances in pharmacologic, non-pharmacologic and technology-assisted treatment options. And if so, can those who manage to avert the course, proceed unhindered with their onward life and health journey?*

Introduction

Disorders of glycemia exist on a continuum. Pre-diabetes (impaired glucose regulation) is known to be reversible. But in recent years, despite initial scanty evidence, there is mounting data that suggests some reversibility in established T2DM, particularly in those with short duration.

There is good motivation to reverse the metabolic e f ects and subsequent major complications of diabetes, both for the individual and society. Diabetes causes signi f cant morbidity and premature mortality. It is a burden on health care systems and costly to treat – with international f gures showing medical costs for people with diabetes are two-to-threefold greater, when compared with those without diabetes.[1] Approximately half of T2DM patients will require insulin therapy within 10 years of their diagnoses. This results in calls by the diabetic care community to advocate that reversal should be included as a treatment goal from early on in the management of the disease, rather than conceding to the fact progression is always inevitable.[2] Like many other chronic impairments, the impact of diabetes becomes increasingly irreversible and consequential over time.

This article aims to address proposed de f nitions of T2DM remission – albeit there is currently a lack of consensus, to examine the available evidence regarding the feasibility of T2DM remission including the mechanisms involved, and to consider the implications on macro- and microvascular risks by answering the following questions:

1.

Despite earlier evidence suggesting remission is possible, it is only as recent as 2016 that reference to T2DM reversal was added to the World Health Organization (WHO) Global Report on Diabetes.[4] There is currently no consensus on the criteria for remission of diabetes. In order to facilitate any data capturing and research efforts, as well as informing resource allocation, clinical care and monitoring outcomes, some consensus would be important to establish. Lack of consensus impacts existing evidence due to lack of standardization.

Recommended criteria are listed in Table 1. The American Diabetes Association (ADA) thresholds (last updated in 2009) for pre-diabetes and diabetes are used, respectively, for partial and complete remission in the absence of active anti-diabetic therapy. Prolonged remission is defined by 5 years or longer persistence of this status.[5] However, a recent position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS) suggests a single definition, using the higher WHO threshold for diabetes as its defining biochemical criterion sustained over a shorter period, including the need for weight loss. Their rationale is well set out in their position statement.[3] The other criteria in the table have been used in studies or proposed by other groups.

Remission does not apply to those with Type 1 diabetes. Also, it is not widely reported in children with T2DM, in keeping with the more aggressive pathophysiology in this age group, where it is not uncommon to see rapidly progressive beta-cell destruction and early onset vascular complications.

What has the journey revealed so far?

While the significant prevalence and association of obesity with T2DM undoubtedly makes it the most modifiable risk factor in terms of both disease preven-

Table 1: Diabetes Remission - Proposed Criteria

	Criteria for Remission				**Confirmatory Maintenance Duration**
		HbA1C	FBG/OGTT*	Meds	
ADA Consensus Group[5]	Partial remission (no longer having diabetes)	< 6.5% (< 48 mmol/mol)	5.6-6.9 mmol/L	None	1 year
	Complete remission (no longer having pre-diabetes)	< 6.0% (< 42 mmol/mol)	< 5.6 mmol/L	None	1 year
	Prolonged remission	< 6.0% (< 42 mmol/mol)	< 5.6 mmol/L	None	At least 5 year's duration
ABCD and PCDS[3]		< 6.5% (< 48 mmol/mol)	5.6-6.9 mmol/L	None	6 months
UK Research Group: McCombie et al[6]		< 6.5% (< 48 mmol/mol)	< 7 mmol/L and 2-hour OGTT < 11 mmol/L	None	Two non-diabetic tests at least 2 months apart, then renewed annually
Buchwald et al	Sustained remission after bariatric surgery	< 6.0% (< 42 mmol/mol)	< 5.6 mmol/L	None	None
*FBG – fasting blood glucose, OGTT – oral glucose tolerance test					

Significant and sustained weight loss is required to reverse diabetes and should be actively communicated and encouraged as soon as possible to all those diagnosed with T2DM. In fact, prevention and treatment should arguably not be considered separately.[7] Weight loss increases peripheral insulin sensitivity. Weight loss is also associated with extended life expectancy for people with diabetes. Studies following weight-loss surgery or dietary calorie restriction have provided insight into the time course of the underlying pathophysiology behind T2DM reversal.

Fasting plasma glucose levels normalize within a week of a significant negative calorie balance, as a result of the substantial fall in liver fat content and as normal hepatic insulin sensitivity recovers, even without a change in the insulin resistance of muscle. Inappropriate glucose release by the liver in the face of normal or high blood glucose caused by liver insulin resistance is a major reason for raised glucose in diabetes.

Similarly, sustained caloric restriction reduces pancreatic fat content, allowing the reactivation of beta-cells from the residual pancreatic reservoir to restore insulin secretion. Some of the lost beta-cell capacity seen in established T2DM has the potential to be reactivated, as pancreatic fat content reduces and elevated glucose normalizes. The size of this pancreatic reservoir is thought to influence the ability to achieve remission and may help to explain why some can achieve remission and others cannot.[8,9]

In community settings, standard of care remission rates are very low. In the absence of bariatric surgery, a large US retrospective cohort study using the ADA remission criteria found the 7-year cumulative incidence of partial, complete or prolonged remission with standard of care management was 1.47%, 0.14% and 0.007%, respectively. The 7-year cumulative incidence of achieving any remission was 1.60% in the whole cohort and 4.6% in the subgroup with new-onset diabetes (< 2 years since diagnosis).[10]

Currently, the evidence supports three ways of achieving diabetes remission: intensive lifestyle adjustments, including both low-calorie (energy-deficient) diets and low-carbohydrate (macronutrient composition) diets, and through bariatric surgery.

Bariatric surgery has been recommended by an international diabetes consensus group for the treatment of T2DM since 2016. Low-carbohydrate diets and short-term caloric restriction to aid weight loss are recommended in the ADA and European Association for the Study of Diabetes (EASD) guidelines, but only as part of the treatment and with reversal not being specifically addressed overall.

Low-calorie (energy-deficient) diets

Calorie restriction is associated with weight loss and hepatic and pancreatic fat reduction, as well as improved glycemic control. Although this might be said for many diets, one of the criticisms of this approach is that it is difficult to achieve and not sustainable. Resulting micronutrient deficiencies

remission with dietary interventions, the following points are important to bear in mind:

- Studies' lack of standardization makes comparison and analysis a challenge.
- Most studies have been short-term, with few exceptions.
- The DiRECT trial hopefully can demonstrate long-term follow-up of low caloric eating, which is still lacking for low-carb diets.
- Sustainability is the most vexing problem.
- There are potential adverse effects of the diets.
- Any diet is likely more effective when coupled with a regular exercise program.
- On-going motivation, encouragement and behavioural change are crucial elements for success.

Surgery

The earliest evidence of the potential for T2DM reversal came from bariatric surgery studies. Various surgical procedures exist: Roux-en-Y gastric bypass (RYGB), adjustable gastric band, sleeve gastrectomy or duodenal switch. RYGB and sleeve gastrectomy are the most commonly performed procedures in the US, with sleeve gastrectomy arguably having the best outcomes. Even the least invasive method is superior to intensive medical therapy, and surgery is generally considered the most optimal method for reversing diabetes both in terms of effect and durability, particularly in those with higher BMIs. Where resources are available, surgical management has been added to

Additional benefts of remission would include increased well-being, lower insurance costs, and reducing the number of medications required. While the latter may not necessarily always be the end goal, and despite not meeting the definition of remission, discontinuing one or more medications may mean fewer side effects, as well as cost savings. Moreover, newer diabetes drugs such as GLP-1 agonists and SGLT-2 inhibitors have shown significant additional benefts in terms of cardiovascular and renal protection, such that their discontinuation, particularly until longer-term implications are more well established, might not be indicated or advisable.

While remission is not achievable for all those with T2DM, in terms of predictors, current evidence would suggest it is more likely achievable in those adults with a diagnosis of T2DM within 10 years of their diabetes diagnosis. Of note, the DiRECT remission study only included people who had diabetes for 6 years or less and were not on insulin. This prospect should encourage remission as a specifc treatment goal very early on in the management of a patient, given that over time beta cells do lose their ability to produce insulin. In the Look-AHEAD trial, greater weight loss, lower baseline HbA1C (better glycemic control), shorter duration since T2DM diagnosis, and no baseline insulin use predicted higher likelihood of remission.

Negative predictors of remission include lower BMI, advanced age and decreased endogenous insulin production measured by low C-peptide levels. As previously mentioned, these predictors might be important to note from a risk assessment point-of-view, in terms of those who might have a better chance at success.

The degree of weight loss needed to achieve remission is also unclear. Moreover, Type 2 diabetics are not always obese. T2DM develops at a lower BMI in Asian populations but probably with similar body fat content. It is thought that increased hepatic fat is a major driver in Asian T2DM. The Reversal of Type 2 diabetes Upon Normalization of Energy intake in non-obese people (ReTUNE) project is under way to answer the question of how and whether remission can be achieved in people with T2DM who are not obese.

Exercise, either aerobic or resistance training, is an effective enhancer of reversal together with calorie restriction; however, it is not effective in isolation. Sustainability of the exercise regimen is key.

Even those who achieve remission need to continue to be screened for diabetes complications. The effects of elevated glycemic metrics, even at levels below the T2DM diagnostic criteria, can impact outcomes.[16] Annual screening for nerve, renal and eye damage for at least 5 years is recommended, with a potential reduction in the frequency of screenings after that. Co-morbid cardiovascular risk factor screening and management must also continue.

Simply put

Remission is not a quick fix.

It requires commitment to making long-term healthy lifestyle changes to maintain weight loss and remission. It has been stated, "The promise of reward and praise for goals achieved are key elements in behavior change strategies."[6] Dedicated and ongoing encouragement would help drive motivation and permanent change, in addition to helping to destigmatize the diabetes label and boost a sense of personal achievement. However, this kind of encouragement is inconsistently

the metabolic disorder, established vascular disease may or may not continue to progress. It is known once diabetes is present for 5 to 7 years, extra mortality and cardiovascular event rates are already established. Where any secondary complications have already manifested, regardless of whether diabetes is put into remission or not, risk assessment needs very careful consideration, especially for living benefits.

At this stage, it is prudent to individualize assess-