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 traffic 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 effects and subsequent major complications of diabetes, both for the individual and society. Diabetes causes significant morbidity and premature mortality. It is a burden on health care systems and costly to treat – with international figures 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 definitions 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. What evidence is there supporting the different ways to achieve remission?
2. How sustainable is the new metabolic state?
3. Is there any evidence to support an associated reduction in diabetes complications?

The final section will address possible implications for risk assessment.

Definition and scope

Remission is defined as the absence of signs and symptoms of the disease. Cure is defined as the restoration of health and no evidence of the disease process by whatever criteria was used to diagnose the disease or condition.[3]

The use of the term diabetes "remission" is preferred, as it best reflects the improved symptoms and biochemical status. In some cases, it even removes the need for treatment but without minimizing the need for ongoing follow-up and management, given the lifelong risk of relapse at any time in the future. Moreover, there is insufficient evidence at this time to suggest this reversal can be permanently achieved, hence any reference where a "cured state" is implied may be inappropriate, if not inaccurate. For the purposes of additional clarification – remission describes the status, while use of the term "reversal" is used when referring to the process.

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 prevention and management, nutrition and weight management remain incredibly controversial topics. It is well established that weight management is a cornerstone of metabolic health maintenance and weight loss can reverse the underlying pathophysiology, improving and even normalizing the metabolic derangements. There are several additional obesity dependent and independent benefits of an improved diet with effects on blood pressure, lipids and apolipoproteins, endothelial function, coagulation and inflammation.

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 require supplementation and monitoring.

One of the most notable studies of a structured low-calorie weight loss program is the DiRECT trial (Diabetes Remission Clinical Trial) which involves a community-based primary care cohort of 306 T2DM patients in the UK. Results from this study have been very encouraging. Intake was restricted to 850 calories per day for 3 months followed by 2 to 8 weeks of food reintroduction, together with a gradual build-up of exercise and ongoing monthly reviews.

After 1 year, 46% had achieved remission vs. only 4% on a standard diabetic-guideline diet. After 2 years of follow-up, 70% of those in remission at 1 year maintained their remission status. Remission was closely related to weight loss with none of those who gained weight during the study achieving remission, but with 86% of those who lost more than 15 kg achieving remission. This trial is still ongoing, with 4 years of follow-up planned.

A large randomized lifestyle intervention study involving overweight and obese T2DM patients – the Action for Health in Diabetes or Look-AHEAD trial – restricted calories to 1,200-1,800/day. This study showed better weight improvement and more favorable glycemic levels at both 1 and 4 years in those in the intervention arm, compared with the control group who received diabetes support and education (DSE). Of note, despite being three to six times higher than the control group, remission rates in the intervention arm did decrease over time.

Long-term impact on maintenance of weight loss and associated glycemic improvements and health consequences of intense calorie restriction remain unknown. There have been reports of a reduction of neuropathy and reduction in retinal complications; however, the evidence is sparse and conflicting, such that ongoing follow-up, especially eye examinations, is still strongly advised.

Low-carbohydrate (macronutrient composition/ restriction) diets

Evidence of the benefits of low "carb" diets on weight loss and glycemic control continues to emerge, despite this being one of the earliest approaches to diabetes therapy. However, the heterogeneity in the approach and definitions across studies limits the ability to fully examine T2DM reversal.

Nonetheless, carbohydrates are undoubtedly the macronutrient with the greatest impact on insulin and blood glucose levels. As far as these diets are concerned, both quality and quantity are important considerations. There are several different approaches to low-carb diets that fall into this broad category. This has made the comparisons of study results a challenge, but overall, the greatest benefits have been associated with the lowest carbohydrate intake.[10] Table 2 shows suggestions for definitions of the different low-carbohydrate diets.[11] The approximate carbohydrate intake before the obesity epidemic was 43%.

Of the randomized trials in a review of low-carbohydrate diets by the ADA, half reported greater improvements in HbA1C and reduction in medication use compared with (predominantly) low-fat comparison diets.[12] Calorie reduction was also often coincident with carbohydrate restriction in many of the studies. While some researchers have suggested HbA1C can improve in the absence of weight loss with a low-carbohydrate diet, lower HbA1C levels as a direct result of a reduction in carbohydrate consumption, while beneficial, does not address the beta-cell dysfunction. Therefore, this does not reverse T2DM pathophysiologically or prevent disease progression.[13]

Ketogenic diets (VLCKD) result in the use of fat as an energy source, which accelerates weight loss in some. The impact of these diets on cardiovascular health is an area of contention. While studies have not found adverse lipid profiles associated with low-carbohydrate diets in either diabetic or non-diabetic populations in the short term, the long-term effects are unclear. Monitoring of lipid levels is advisable.

Hypoglycemia is a potential risk of low-carbohydrate diets. Transient elevations in uric acid with associated exacerbations of gout and kidney stones have been documented. Higher protein content in low-carb diets may potentially impact renal function. Evidence to-date in patients with diabetes have not shown any worsening renal function after short-term follow-up, but the long-term effects on chronic renal disease are unknown. The long-term effects on cardiovascular disease also need further evaluation.

Overall, carbohydrate tolerance must be individualized for optimal impact, as carbohydrate tolerance varies between individuals and even in individuals over time. Long-term adherence remains a crucial focus point with this approach, highlighting the important, yet undetermined, impact of the behavioral changes required. The lack of longer-term follow-up studies on these outcomes from a long-term risk perspective remains a limitation. An additional challenge is comparing studies involving different interventions, given the varying definitions and study designs with very few systematic reviews, making it difficult to draw conclusions from older studies.

A word about diets

- Significant short-term energy restriction eating may affect clinical remission via several mechanisms: reduction in liver and pancreatic fats, improved insulin sensitivity, and restored insulin production via beta-cell recovery.
- For low-carb diets, the lower the carbohydrate content, the greater the glycemic improvement. Many are ad libitum diets, but often result in reduction in average energy intake; thus, there is much overlap between lower calories in low-carb diets. It has been observed that low-carb eating is effective in lowering glycemic levels even without significant weight loss – at least in the short term.
- Even with evidence to suggest effective glycemic improvement, reversal of biochemical status and

Table 2: Low-Carbohydrate Diets

Very low-carbohydrate ketogenic diet (VLCKD) "Keto" diet	Carbohydrate 20-50 g/day or < 10% of the 2,000 kcal/day diet, whether or not ketosis occurs (these low levels induce ketosis in most people)
Low-carbohydrate diet	Carbohydrate < 130 g/day or < 26% total energy ADA recommends this as its absolute minimum "Low Carb, High Fat" or "Low Carb, Healthy Fat" (LCHF) approach
Moderate-carbohydrate diet	26%-45% total energy
High-carbohydrate diet	> 45% total energy

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 guidelines as an option for some with T2DM.

Drawbacks of this approach, however, include surgical complications (rates as high as 25%), malnutrition, leaks or bowel obstruction, dumping syndrome, severe hypoglycemia, and the need for radical post-surgical lifestyle modification. Other than gastric banding, bariatric surgery cannot be reversed. Treatment cost can be a limiting factor, although economic analysis has suggested surgery is cost-effective in the longer term, especially in obese patients. Long-term outcomes overall depend on many factors.

Remission, in the context of bariatric surgery, is related to the degree of weight loss, although other enteroendocrine mechanisms are likely at play, including the release of gastrointestinal hormones (impacting feeding behavior) and changes in the gut microbiota and their metabolome – given that weight loss does not occur immediately following surgery. Calorie restriction also plays a role. The role of the gut microbiome is an area of ongoing research and interest. It has led to discussions that manipulating these beneficial effects, without the need for surgery, might even be possible in the future.

Surgery rapidly improves blood glucose, reduces the need for medication in up to 80% (range of 40% to 80%) of patients within the short term in some studies, with an additional 15% demonstrating partial improvement despite requiring medication. Randomized trials show slightly lower remission rates than observational studies.[14]

Long-term T2DM remission data indicates sustained weight loss is a predictor of better outcomes; however, it shows less durability over time. The percentage of those in remission diminishes at a rate of around 7% to 15% per year. The prospective Swedish Obese Subjects (SOS) study reported a 72%, 36% and 30% T2DM remission rate for RYGB after 2, 10 and 15 years following surgery, respectively. A recent review of outcomes states half of remitters have relapsed after 20 years.[15] Additional analysis is required to discover the reasons for relapse.

Better pre-operative beta-cell function is the strongest predictor for remission. Clinical correlations of this include diabetes duration, glycemic response to lifestyle and oral medication, and use of exogenous insulin. The latter is likely the most significant factor. The longer someone has been on exogenous insulin, there is little chance they will no longer be diabetic, irrespective of the amount of weight lost. The importance of identifying those who might have better outcomes could be a useful prediction tool, from a risk assessment point-of-view.

Post-surgical follow-up requires B12, iron and vitamin D surveillance to prevent treatment-induced extra mortality or morbidity. In addition, the behavioral and psychosocial aspects and outcomes of weight loss surgery require further investigation.

Clinical management and risk assessment considerations

An important consideration from a long-term risk perspective is the impact of remission on diabetes complications. It is known from previous trials that clinical outcomes for people with T2DM are better with lower HbA1C levels. Even if remission is not achieved, any reduction in HbA1C and/or weight loss, through whichever means, is likely to be hugely beneficial and lower the risk of associated co-morbidities and long-term complications. Reduced cardiac events have been observed in patients with T2DM after bariatric surgery. However, no study has yet examined outcomes for people who achieve remission.

Additional benefits 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 benefits 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 specific 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 provided in various markets and requires consideration during risk assessment.

Remission is not a cure.

A concern might be whether one develops a false sense of security if diabetes is thought "cured," including less attention paid to other risk factors such that education and strict maintenance of other primary prevention targets needs to be diligently followed up. Integrated programs may help to track progress over time and offer a more dynamic solution. In time, these advances will likely improve clinical care and be beneficial overall, but this too remains to be realized and quantified.

Diabetes is a long-term disease that is the eventual manifestation of many dysfunctional mechanisms. It is possible to reverse the manifestation, but what about the underlying mechanisms which include molecular, epigenetic changes and long-term metabolic stresses? Some are reversible and some – probably not. Long-term reversal is reliant upon on-going lifestyle treatment, which means a person is never in true remission but only in long-term "control." Weight loss removes the precipitant but not the underlying genetics, which are likely "primed" and remain open to being expressed again. Re-expression is more likely in those with a very strong family history, recurrent weight gain (even at moderate levels), with pregnancy and with other known precipitants. Weight loss, in those converted from very obese to obese or even overweight, is unlikely to be in the metabolically healthy obese category in the first place.

Given the potential to accumulate vascular damage that might not be reversible, despite normalization of

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 assessments. What will be important to assess is the duration over which the proposed insured was definitively diabetic, control during that time, and whether any complications or end-organ damage was recorded. While diabetes is being diagnosed increasingly at the early stages before any microvascular complications develop, screening for diabetes is not universal, such that some applicants might have had diabetes for a few years before the diagnosis is even made. On the other hand, more people are already on statins and anti-hypertensives at the time of their diabetes diagnosis.

The crucial issues are the long-term stability and permanence of the remission. In those without established complications who have documented evidence to suggest remission by whichever means it was achieved, looking for positive predictors of sustained remission and good compliance is paramount. Reversing the biochemical aspect of hyperglycemia, lipids and liver dysfunction is possible, but the element which remains unknown is long-term behavior – a factor that is less tangible and needs to be predicted in underwriting.

The documented duration of remission would inform how stable the newly developed status is, and perhaps, how likely it is to remain. If we consider the ADA criteria in Table 1 above, at least 5 years of stability would be necessary to have achieved "prolonged remission"; however, this would not be the only consideration. Any assessment would require a thorough assessment of not just the applicant's current status, but also their journey up to that point, including a projection of what might emerge in the future.

Conclusion

With many impairments increasingly impacted by advances in medicine, it is necessary to stay abreast of the prevailing literature and make adjustments in risk assessments, when warranted. It is prudent to ensure the body of evidence is well validated and consistent. There is still much regarding the long-term benefits vs. negative consequences of T2DM remission that remains to be explained. It may be like driving through the mist with the warning lights on, but hopefully visibility will improve and navigation will become easier. Diabetes reversal presents an exciting, yet challenging intersection for risk assessors. Based on current evidence, the question remains – is this just a detour which ultimately leads to the same destination in terms of adverse outcomes, or is this an opportunity to turn in a completely new direction with better long-term prospects? Medical and technology-assisted advances, behavioral insights, and a relentless pursuit to apply the latest research prudently in navigation systems will ensure optimal solutions to this evolving paradigm.

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