

Is lasting remission feasible in the real-world setting? No!

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This article summarises a debate at the 59th EASD Annual Meeting 2-6 October 2023, Hamburg, Germany at which Professor Khunti spoke against the motion and Professor Taylor spoke for the motion (See page 95)

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Br J Diabetes 2024;24(1):97-98
<https://doi.org/10.15277/bjd.2024.453>

In considering whether lasting remission of type 2 diabetes (T2DM) is feasible in the real-world setting, we must first consider what we mean by 'lasting' remission, and if it is feasible to achieve this for large numbers of people. Unfortunately, there is a lack of consensus internationally on how remission is defined. A systematic review of 178 studies of T2DM remission reported 266 different definitions of remission.¹ The most recent consensus report from the American Diabetes Association defines remission as an haemoglobin A1c (HbA_{1c}) <6.5% (48 mmol/mol) three months after cessation of glucose-lowering therapies.² However, one aspect that such definitions ignore is the underlying pathophysiology of T2DM. Natural history data show that diabetes is a progressive disease. For example, the longest running study on the prevention of diabetes, the Da Qing study, reports that 80% of patients still go on to develop diabetes after 20 years.³

One key means of achieving remission is lifestyle intervention and adherence to a low-energy diet (LED). Numerous studies have trialled an 800-900 calorie diet for 8-12 weeks through meal replacement.⁴ At year 1 remission in the DiRECT study was achieved in 46% of patients, dropping to 36% in year 2 and an estimated 7% in year 5 (data presented at Diabetes UK 2023). Remission in the Look Ahead study was 16% at year 1, and around 4% at year 4.⁵ Long-term remission is clearly difficult to achieve, and in addition we must also consider that substantial weight re-gain following cessation of a LED is commonly reported in trials. This area is further complicated by methodological problems and reporting bias in weight maintenance data. Adherence to dietary interventions is challenging for various reasons. A number of circulating hormones are altered; these mediate appetite and encourage weight regain, increased hunger, increased appetite, and increased preference for energy-dense foods. Interventions such as bariatric surgery and glucagon-like peptide-1 (GLP-1) agonists target some of these responses.

In relation to GLP-1 agonists, there are good supporting data. For example, in the SURMOUNT-2 study of 938

Key words: type 2 diabetes, T2DM, remission, LCD

randomised patients, 80% of people in the tirzepatide arm achieved remission at 72 weeks through once-weekly injections.⁶ In the STEP-2 study, some 1,200 patients were randomised to receive semaglutide (two dose arms) or placebo: 67% achieved remission (HbA_{1c} < 6.5%) in those receiving the higher semaglutide dose (2.4 mg once per week) at 68 weeks.⁷ However, this may not strictly be defined as remission, as these patients are in receipt of therapy, and in the real-world setting adherence rates to GLP-1 agonists are low.

Remission with metabolic surgery may also be possible and may bring cardiovascular outcome benefits.⁸ The long-term follow-up in the SOS study reported remission rates of 72% at two years, reducing to 30% at 15 years.⁸ However, there are a number of barriers to using metabolic surgery as a method for remission. It cannot be implemented at scale as a population level intervention, and there are long-term complications including psychological issues, weight regain, fractures and hypoglycaemia.

Likelihood of remission

In the real-world setting, we have examined remission of T2DM in routine care. Analysis of a whole of England database (n=2,297,700) of people with T2DM between 2007 and 2018 demonstrated that around 1.7% of patients met the criteria for remission.⁹ This suggests remission is unlikely in a real-world setting, except for a small group of people who we identified as having lost a significant amount of weight shortly after diagnosis.

For those who do achieve remission, there may still be health implications, and in some cases a false sense of reassurance. Data we published last year on coded remission showed that there were significant reductions in routine annual checks for HbA_{1c} and cholesterol and a 24% reduction in foot examinations.¹⁰ A recent Danish registry data study in 14,000 people with T2DM showed that those in remission who did not receive any glucose-lowering therapies had a twofold increased risk of major adverse cardiovascular outcomes (MACE).¹¹

Defining remission solely based on glucose levels arguably overlooks long-term outcomes. The crucial factor lies in sustaining weight loss over an extended period and minimising both macro- and microvascular complications. Relying solely on glucose-centric criteria may falsely reassure patients that their diabetes is no longer a concern. While bariatric surgery offers the most significant initial weight loss and long-term remission, it remains an inaccessible option for the majority of individuals with T2DM. We do have alternative therapies at our disposal, although they may not qualify as remission definitions since people with diabetes depend on ongoing treatment. GLP receptor agonist trials indicate the potential to achieve an HbA_{1c} reduction to 6%.

Currently, intervention data reveal that for very low-calorie diets, there is a lack of information regarding microvascular and cardiovascular benefits and cancer outcomes. However, there is evidence of improved quality of life post-surgery. Lifestyle interventions establish improved microvascular, cardiovascular and cancer benefits, along with enhanced quality of life, although data are lacking for these outcomes. As regards pharmacological interventions, there are documented benefits in terms of microvascular and cardiovascular improvements, as well as enhanced quality of life, but specific data on cancer outcomes are also currently lacking. The other major issue is inequity. The DiRECT trial showcases evidence of HbA_{1c} reduction, with its participants mainly comprising a white population residing in northern regions of UK. It is worth noting that the DiRECT trial intervention lacks representation from many ethnic minorities.

Prioritising wellbeing

It is arguably best therefore to revisit the perspective of individuals living with diabetes. What are their desires? An insightful qualitative study suggests that people with diabetes do not wish for lifestyle restrictions, a diminished quality of life or a loss of control.¹² They experience anxiety and frustration and are naturally fearful of long-term complications; instead, they aspire to lead long and happy lives. As outlined above, there are interventions aligning with these aspirations. It is crucial therefore to prioritise the wellbeing of individuals with diabetes, understanding their preferences and striving to provide them with a fulfilling and extended life.



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Conflict of interest KK has acted as a consultant, speaker or received grants for investigator-initiated studies for AstraZeneca, Bayer, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, Pfizer, Roche, Daiichi-Sankyo, Applied Therapeutics, Emecta and Nestle Health Science.

Funding KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).

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