

Is lasting remission feasible in the real-world setting? Yes!

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This article summarises a debate at the 59th EASD Annual Meeting 2-6 October 2023, Hamburg, Germany at which Professor Taylor spoke for the motion and Professor Khunti spoke against the motion (See page 97)

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The widespread attention to dietary weight loss for remission of type 2 diabetes (T2DM) arose from the solid basis of a new understanding of the physiology of glucose and lipid metabolism. The development of magnetic resonance techniques to quantify metabolism inside the liver and pancreas allowed the 2008 twin cycle hypothesis to be tested.¹ The smaller the study, as determined by prior power calculation, the larger the effect size and the more likely that it will impact upon management of individuals in the clinic. The Counterpoint study required only 11 participants to achieve highly significant results: effective dietary weight loss returned to normal glucose metabolism in short-duration T2DM. This outcome depended upon a dramatic fall in liver fat content, the return to completely normal liver insulin sensitivity, a major decrease in liver fat export and a decrease in pancreas fat content.²

To test the hypothesis, a sure-fire method of achieving around 15kg weight loss had to be devised. On the basis of information from patients about why they found it difficult to lose weight, acquired over some decades in the clinic, it was essential to minimise hunger and to avoid the cumulative burden of day-to-day choices about what and how much to eat. The time-limited low-calorie approach proved successful and was used in the subsequent studies (Table 1). The Counterbalance study established that the return to non-diabetic metabolic health lasted for at least six months after stopping the low-calorie diet and returning to normal eating (with emphasis on avoiding weight regain).³ In the real world of primary care, the DiRECT RCT demonstrated 46% remission of T2DM at 12 months and 36% remission at 24 months.⁴ Importantly, this study also showed that the underlying change in physiological function revealed in Counterpoint lasted for at least two years after return to non-diabetic blood glucose control provided that weight regain was not excessive.⁵ Those who were initially in remission but gained too much weight were observed to lose beta cell function as pancreas fat content returned to baseline.

During the two-year DiRECT RCT, any weight regain was managed according to a pre-planned rescue package to get

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weight back on target, as an acute life stress was often responsible. However, as reflected by the five-year follow-up data, people continued to live in the same obesogenic environment and weight regain continued up to year 3 before plateauing.⁶ The weight loss from baseline remained impressive at an average of 6.1 kg below baseline, but this was inadequate to maintain remission in most people. In contrast, the group who remained in remission had an average weight loss of 8.9 kg. These long-term remissions amounted to 26% of those in remission at two years, or 13% of the whole group followed up. Importantly, T2DM occurs when an individual exceeds their personal fat threshold – irrespective of body mass index – and weight loss within the ‘normal’ range achieves lasting remission.⁷

Providing support

The preceding paragraph illustrates very clearly that the answer to the debate question is ‘yes’. Long-term remission of T2DM in the real world is feasible – but requires support. This is beneficial for individuals and for health care economics, as shown by the more than 50% decrease in serious adverse outcomes by intention-to-treat analysis of the whole study population.⁶ The advantages go beyond conventionally regarded complications of diabetes, with the number of new cancers (all known to be weight-related) being 8 in the conventionally treated group compared with 1 in the weight loss group. This protection from cancer is reflected in the recent metabolomic examination of cancer-related plasma proteins.⁸ The wider health benefits of an effective weight management programme are impressive, quite apart from not having to take hypoglycaemic drugs and relief from living under the shadow of diabetes.

The emphatic ‘yes’ to the debate question highlights the major matter of how to maximise avoidance of weight regain. The approach to management of an individual is summarised in Figure 1. In the follow-up period of DiRECT, the use of relapse management was not as planned, and this partially explains the degree of weight regain. However, until regulatory controls are

Table 1. The Counterpoint study tested the Twin Cycle Hypothesis and set in train a series of studies elucidating the aetiology of T2DM and hence its clinical management

Understanding T2DM and long term remission – 5 critical studies	
2011 Counterpoint	Rapid return to normal on an 800 kcal/day diet; mechanisms defined
2016 Counterbalance	Remission lasts at least 6 months
2016 Pancreas	Intrapancreatic fat falls with acute weight loss only in T2DM and non in non-DM
2017 DiRECT	Remission is possible in routine Primary Care and is durable; underlying mechanisms confirmed
2023 ReTUNE	In people with BMI 21-27 and T2D - 70% remission brought about by same mechanisms

set in place to limit the addition of sugar to processed foods such as ready meals and take-aways the obesogenic environment will limit effectiveness. The lack of effect of hidden sugar in contributing to satiety is well recognised. The diversionary tactics of focusing upon exercise, as exploited in the undermining by a major soft drinks manufacturer of one nation's anti-obesity strategy, deserve to be widely recognised.⁹ A mouthful of food (especially if sugar-loaded) will undo a tolerable period of vigorous exercise. Clearly, increased physical activity is important as a component of avoiding weight regain but it should not be mistaken for an effective solution to losing weight for most adults.

In the real world, case reports are useful in understanding what is feasible. The individual reported by Peters and colleagues in 2016¹⁰ as achieving remission and avoiding amputation remained in remission for nine years, despite a temporary episode of weight regain following a change of work environment and recurrence of diabetes, before being lost to follow-up during the recent pandemic. Reading the book 'Fixing Dad',¹¹ or watching the associated TV series, conveys the really important role of family in supporting weight loss and then weight stability, with remission for at least seven years and also avoidance of amputation. The dramatic 12 year data from the Look AHEAD study underscore this point, with a 40% decrease in cardiovascular disease even if remission is for one year only.¹²

Lasting remission is not only feasible – it is life-changing.



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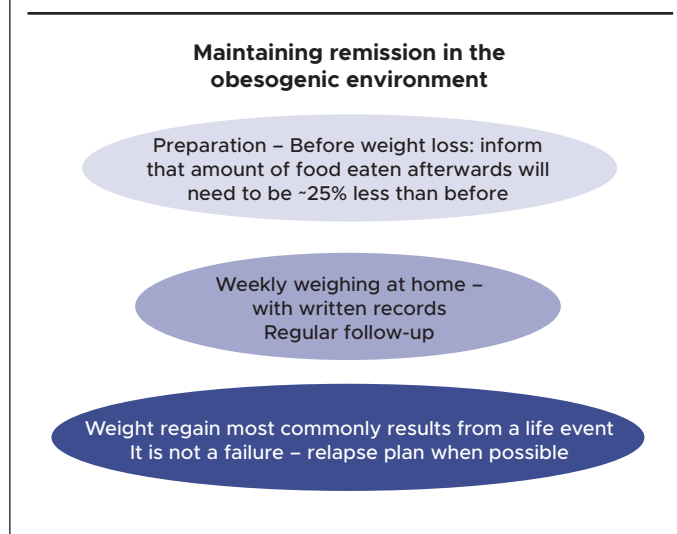
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Figure 1. Strategy to minimise long-term weight regain after weight loss. The infinitely more important modification of our current food environment requires regulatory change.



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