

Reversing type 2 diabetes

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Type 2 diabetes is widely regarded as a chronic, incurable disease. The view is based upon the outcome of large studies such as the UK Prospective Diabetes Study. The steady deterioration in control over several years necessitates an increase in the number of oral agents and eventually insulin therapy. This deterioration in control over time is related to an inevitable, steady decrease in beta-cell function. Treatment typically focuses on minimising the risk of complications.

However, reversal of type 2 diabetes following bariatric surgery has long been recognised.¹ More recently, the rapidity of return to normal of plasma glucose has been described² and, because this precedes any significant weight loss, it has become widely believed that a direct surgical effect on the gut brings about this effect by changing incretin secretion.^{3,4} This is so despite the observations of the pioneer of bariatric surgery, Walter Pories, who pointed out long ago that an inadvertently performed sham operation (opening the abdomen only) had the same early effect on normalising blood glucose as that of gastric bypass.¹ The profound change in daily energy intake from the day of surgery onwards has been rather overlooked. At a body weight of 150kg preoperatively, the mean daily requirement of energy at steady weight will be approximately 3200kcal⁵ and this will fall close to zero from the morning of surgery for several days. These considerations led to the hypothesis that the dramatic fall in energy intake was the sole cause of the reversal of diabetes and, further, that the sequence of events involved would throw light on the basic cause of type 2 diabetes.⁶ It was postulated that excess fat in the liver would trigger a cycle of increasing glucose output for the liver. It would also initiate a cycle of decreasing insulin response to glucose. The latter would be caused by increased triglyceride export from the liver to the pancreas. The Twin Cycle hypothesis required to be tested, and to do this we embarked upon the Counterpoint (Counteracting the Pancreas Inhibition by Triglyceride) study.

The Counterpoint study

Eleven people with type 2 diabetes were studied before and during eight weeks of a 600kcal/day diet.⁷ The study size was based on a power calculation to ensure definitive testing of the hypothesis. After one week of restricted energy intake, fasting plasma glucose had entirely normalised. This was related to normalisation of hepatic insulin sensitivity. It occurred in step with normalisation of liver fat level (a 30% decrease). The early changes were entirely unrelated to insulin sensitivity in muscle. Over the eight weeks of energy restriction, use of a new magnetic resonance technique to measure precisely the level of fat in the pancreas demonstrated that pancreas fat content fell gradually. In step with this, insulin secretion, and specifically first phase insulin response, rose gradually to become normal after eight weeks of the very low energy diet. After the study, the volunteers were given advice about healthy eating with a goal of avoidance of weight gain. Three months after

the study, despite weight gain averaging 3kg, only three out of 10 subjects tested showed blood glucose levels which were just within the diabetic range.

The conclusions of the Counterpoint study are very clear. Firstly, type 2 diabetes is a reversible syndrome. This is so at least in the early years after diagnosis, as volunteers for the study were specifically selected to have had type 2 diabetes for four years or less. Secondly, the characteristic beta-cell defect of type 2 diabetes can be abolished by dietary means alone. The return of normal beta-cell function occurred precisely in step with decrease in the level of fat in the pancreas. This observation fits well with *in vitro* studies suggesting that incubation of beta cells with increased fat concentration prevents acute insulin secretion in response to an increase in glucose concentration.⁸ However, *in vivo* cause and effect require more formal proof before being regarded as fact. Thirdly, dietary energy restriction rapidly decreases liver fat levels and in type 2 diabetes this is associated with a rapid return to normal of hepatic insulin sensitivity. Fourthly, the extent of weight loss required on average to reverse type 2 diabetes is around 15kg.

There is a fifth conclusion. Given the range of intra-organ fat levels observed in the volunteers both with and without diabetes, it is clear that different individuals exhibit different susceptibility to fat accumulation in the vital organs. This 'liposusceptibility' allows simple explanation of the common observation that different individuals develop diabetes when BMI rises above a personal threshold – maybe 35, or maybe 25kg/m² for example. In addition to the liposusceptibility, individuals of the same BMI may store very different amounts of fat in the vital metabolic organs instead of in the metabolically safe subcutaneous depot. Both genetic and environmental factors may govern these tendencies, but this should not cloud the central point: if a person has type 2 diabetes, he or she has more fat in the liver and pancreas than they can cope with.

Longer-term effect of re-establishing normal glucose control

Will the newly re-established normal glucose tolerance be durable? Evidence from the bariatric surgical literature suggests that it will be, providing that weight control is maintained. Observations upon populations suggest that diabetes prevalence mirrors food supply over years or decades. The effect in individuals or populations will be maximised by a high level of daily physical activity.⁹

The effect of type 2 diabetes in bringing about a 50% decrease in beta-cell number is likely to relate to apoptosis, a process promoted by excess fat presence around insulin secreting cells.¹⁰ This is unlikely to have been affected over the period of the Counterpoint study but is likely to be a factor in the long-term development of need for exogenous insulin therapy. If the metabolic abnormalities can be corrected, this process would be predicted to stop, and this concept now requires to be tested in future studies.

What are the practical implications of the observations to date?

The Counterpoint study was not a trial of a potential therapy. The study design was tightly focused upon testing a hypothesis by achieving major negative energy balance over the eight-week period of observation. In particular, it does not prove that use of any one dietary approach is the best way to achieve weight loss and reversal of type 2 diabetes. Clearly, much work remains to be done to establish the most practical way of inducing reversal of type 2 diabetes, and also the most practical way of maintaining normal glucose tolerance once achieved. Nonetheless, until such information is acquired, it would be inappropriate not to use the advance in understanding of the nature of type 2 diabetes to the advantage of our patients. What is reasonable to advise people with diabetes at present?

At the time of diagnosis of type 2 diabetes, and early in the course of the condition, everyone should be informed about the potential reversibility. Clearly, there are caveats, as slow-onset type 1 diabetes, pancreatic diabetes and monogenic diabetes will not reverse and diagnosis of these is usually not made early in the clinical course. However, what should be advised about food? What to eat? A chance observation is relevant. When the Diabetes UK grant which supported the Counterpoint study was announced in *Balance*, one person telephoned immediately to ask to take part. The basic idea behind the study was explained, as was the need for delay until all of the research regulatory matters had been satisfied. Nine months later, she was contacted, tested and found not to have diabetes any more – having taken the message to heart and lost weight by a substantial decrease in portion size (with help from Overeaters Anonymous Great Britain). This was published as a case report¹¹ but there is little else in the literature demonstrating reversal of type 2 diabetes. Most reports of low calorie diets show improvement rather than normalisation of blood glucose control. The Belfast diet study provides an example of reasonably controlled yet persistent diabetes. This study showed that a mean weight loss of 11kg decreased fasting blood glucose levels from 10.4 to 7.0mmol/L, but that this abnormal level was followed by the all too familiar steady deterioration of control.¹² Normal glucose tolerance has been demonstrated after standard energy restricted dieting in 20% of a group of people with type 2 diabetes.¹³ Many clinicians know of a small number of such cases. The present position is that a decrease in portion size by approximately 50% appears to be the most sound initial approach.

For some people, restriction of portion size is difficult and weight loss is more effectively achieved by the use of a very low energy liquid formula diet. The number of people willing and able to undertake such major dietary energy restriction appears to be underestimated by health care professionals. Views are understandably influenced by perceptions about very low energy diets which used to be regarded as unsafe but which are now accepted as a sound approach to weight loss as part of an overall strategy. Contrary to widely held opinions, achievement of major weight loss by dietary energy restriction by use of liquid formula diets is effective and appropriate for some people who find standard energy restriction difficult.

Let's hear the patient perspective

An unexpected result of publication of the Counterpoint study was the intensity and volume of response from people with diabetes. Over 800 emails, letters and phone calls were received about the study. The major theme was of relief at the possibility that type 2 diabetes may not necessarily be a life sentence, and this was coupled with very strong views about the personally devastating effect of the diagnosis of type 2 diabetes. Clearly, these views were expressed by a self-selected group of people who felt very strongly and were motivated to communicate. However, the vital point remains that a substantial number of people are strongly motivated to take action, drastic if necessary, to regain their health. In order to answer the most common questions asked and to provide the practical information requested, our website was extended (www.ncl.ac.uk/magres).

It must be recorded that many individuals expressed frustration at the routine manner in which their doctor, nurse or dietitian regarded the diagnosis of type 2 diabetes. This conflicted with the cataclysmic blow which they personally felt. They were told that the diagnosis was clear and therefore the guidelines will be rolled out. Lose some weight and take this metformin. Get used to it. While all health care professionals dealing with type 2 diabetes would recognise that some people would not wish to disrupt current lifestyle for future health gains and do indeed accept type 2 diabetes as fate, the views of a substantial minority demand attention. Management must be appropriate for the individual. This will come as no surprise to the self-selected group of health care professionals who read this commentary.

Summary

The recently reported data demonstrate unequivocally that the predictions of the Twin Cycle hypothesis are confirmed. Decrease in daily energy supply alone can reverse type 2 diabetes, and this reversal is associated with decrease in fat levels in the pancreas and liver. Concepts of aetiology of type 2 diabetes can now be simplified, as there appears to be a single causative factor – increased fat availability within the vital organs. Type 2 diabetes is a reversible syndrome at least in the early years after diagnosis. The potential gains in health for the individual and the overall economic advantage for society are enormous, even if only a small proportion prove able to alter food intake appropriately. Further work is now required to test practicable management strategies.

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Declaration of interests

There are no conflicts of interest declared.

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References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

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