

Type 2 diabetes: the problem and the solution

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Br J Diabetes 2022;**22**(Supp1):S55-S58

Key words: T2DM, aetiology, pathophysiology, pancreas fat, personal fat threshold, remission

Introduction

The 100 years since insulin was discovered have seen major progress in understanding the aetiology of type 1 diabetes. In contrast, type 2 diabetes (T2DM) remained mysterious until recently. Clinical studies and clinical experience had resulted in widespread acceptance of the apparently lifelong, progressive nature of the condition. Discoveries over the last 16 years have permitted these rationalisations to be discarded and the aetiology of T2DM is not now in doubt. It is a condition of excess fat inside the liver and pancreas which can be countered by weight loss. A turbulent 16 years of study has led directly to a therapeutically useful understanding of the condition. Importantly, this can be tailored to the individual.

Defining the problem

Up to the year 2006, T2DM research in Newcastle had been evaluating the problem of liver insulin resistance and fat in the liver, using the new tool of magnetic resonance spectroscopy. It seemed that the liver insulin resistance typical of T2DM was entirely due to accumulation of fat in the liver. If this could be resolved by weight loss then there was at least a partial solution, given that the fasting hyperglycaemia of diabetes is due to excess production of glucose by the liver secondary to insulin resistance.

But what about the other long-recognised contributor to T2DM, namely decreased post-prandial response to a meal? In 1994 Roger Unger had defined the response of beta cells to a small excess of fat.¹ He had the brilliant idea of taking the intact islets from young rodents who would develop T2DM if overfed and showed that pancreatic islets from young rodents who were genetically similar apart from their susceptibility to develop T2DM were completely resistant to fat exposure. This classical physiology experiment defines the reason why some people develop T2DM and others, even if very overweight, do not develop the condition. The ultimate susceptibility to T2DM is genetically determined within the beta cell. In fact, 72% of people with a BMI over 45 do not develop T2DM.²

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<https://doi.org/10.15277/bjd.2022.366>

Working out how these twin observations on liver and pancreas could fit together took some time, but eventually the Twin Cycle Hypothesis emerged after much scribbling and filling sheets of paper with possible pathways and relationships.³ There was a potentially elegant solution, summarised in Box 1: T2DM might be caused by two vicious cycles interacting, one in liver and one in pancreas. This hypothesis could be tested.

Box 1 The Twin Cycle Hypothesis of Aetiology of T2DM

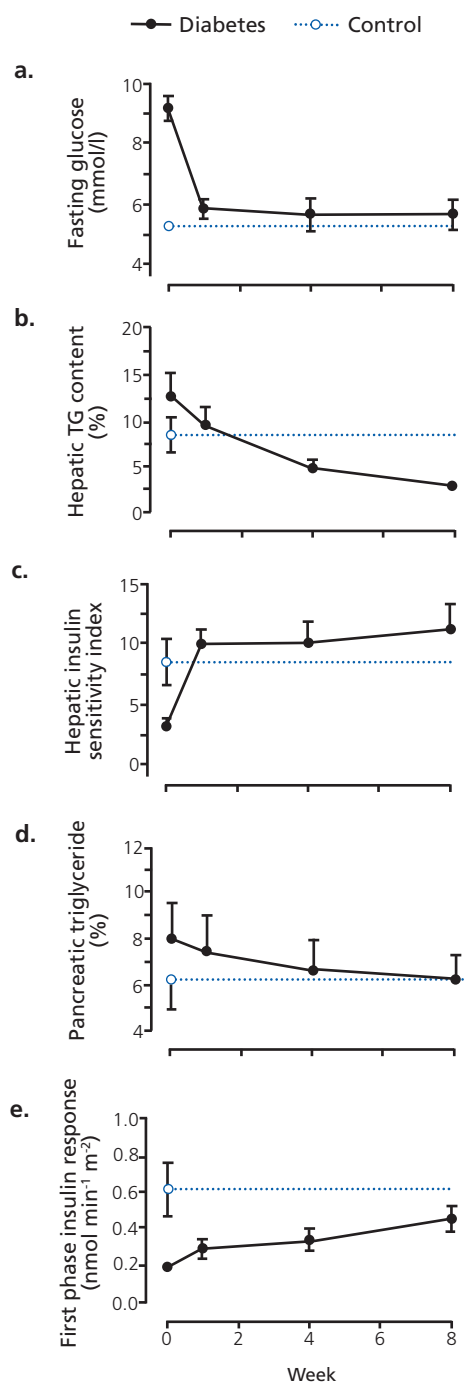
1. Gradual build-up of fat in the liver results from overprovision of calories over a long period, especially in those people who have a tendency to muscle insulin resistance. Such people store almost no mealtime carbohydrate in skeletal muscle, unlike people with normal muscle insulin sensitivity who store around one third of meal carbohydrate in muscle following a meal so it is converted to fat for storage
2. Over many years the liver becomes less and less able to respond to insulin, so glucose production is unrestrained, causing elevated fasting plasma glucose levels
3. The fatty liver also exports more triglyceride than normal. If this cannot be stored in subcutaneous adipose tissue – a metabolically safe storage depot – then it has to be taken up in ectopic sites, including the pancreas
4. The provision of excess fat to the islets decreases ability to produce insulin rapidly after meals in susceptible people
5. The greater post-prandial plasma glucose rise which results further increases rates of lipogenesis in the liver. Consequently, the Twin Cycles are self-reinforcing

Testing the Twin Cycle Hypothesis

The Counterpoint study (Counteracting the Pancreatic inhibition of Insulin secretion by Triglyceride) required a method of reliably producing the 15 kg weight loss calculated to be required to remove the fat from liver and pancreas. Rapid weight loss was necessary for the pressing reason that the Diabetes UK grant for the study was for two years in total. An 800-kilocalorie diet could be nutritionally complete, free from the day-to-day burden of making decisions, by use of one packet per meal of a liquid formula diet plus non-starchy vegetables only. This approach, which became known as the “Newcastle diet”, was originally a tool developed purely to test the hypothesis.

The results were dramatic.⁴ Within seven days of starting the diet and stopping metformin plasma glucose returned to normal (Figure 1), and over eight weeks weight decreased by an average of 15.3 kg. All the predications of the Twin Cycle Hypothesis were confirmed by using magnetic resonance techniques developed specifically for the purpose. The level of liver fat was shockingly high in T2DM and this fell precipitously, accompanied by the return to normal of the initially raised liver glucose production rates.

Figure 1. Change in fasting plasma glucose on commencing an 800kcal/day diet and stopping metformin. The change within seven days was shown to be due to a fall in liver fat content, the return of normal hepatic insulin sensitivity and normalisation of hepatic glucose production. A slower decrease in pancreas fat content was paralleled by a slow increase in beta cell function. Data are from the Counterpoint study, which initiated the worldwide interest in diet-induced weight loss for remission of T2DM.⁴



Plasma triglyceride levels decreased to normal and gradually the pancreas fat content decreased. Most excitingly, both the first phase and the maximal insulin secretion rates improved.

The Counterpoint study was first presented to a scientific meeting at the ABCD Newcastle meeting in 2010. The 2011 publication attracted much interest but great scepticism among experts. Doctors 'knew' that T2DM was for life, and scientists were trapped in a belief system that was slow to change. Not so people with the condition! A tsunami of emails were received requesting how-to-do-it details, and the Newcastle University website on diabetes reversal was created (<https://go.ncl.ac.uk/diabetes-reversal>). A descriptive analysis of the subsequent wave of emails reported that around half the individuals with T2DM followed the advice that ordinary food (but strictly around 800 kilocalories/day) could be used and half used liquid formula diets.⁵ The groups were equally successful in achieving return to a fasting glucose of <6.1%. Importantly, the effect of duration of T2DM upon pancreas recovery became clear. Reversal rates according to diabetes duration were: short (<4 years) = 73%, medium (4–8 years) = 56%, and long (>8 years) = 43%.

The beta cell question

There was great antipathy to the notion that fat could cause the decline in beta cell function, particularly among beta cell experts. This may have been a function of the widespread use of high glucose levels rather than fat to induce and study beta cell stress *in vitro*. The major argument raised was that weight loss might cause decrease in intra-pancreatic fat as an unrelated phenomenon, and it was really the starvation-induced decrease in plasma glucose which brought about beta cell recovery.

To test this, groups of people with or without diabetes but achieving equal weight loss were studied. We showed that the fall in pancreas fat occurred only in people with T2DM. There was no acute fall in fat and no change in insulin secretion in people without diabetes. There is an excess of relatively rapidly mobilizable fat in the pancreas of people with T2DM only. Work by Ann Clarke and Domenico Accili showed that the metabolic stress of excess energy supply *in vitro* produced loss of specialised function of beta cells (de-differentiation) and that removal of excess fat allowed re-differentiation with restored function.^{6,7} The mechanism underlying central problem of T2DM could now be understood. Beta cell death or apoptosis was not relevant. Together with the Twin Cycle Hypothesis it explained why the incidence of T2DM varied with the nutritional state of populations.

Refining the solution

Two major clinical questions arose from the Counterpoint study. First, would it be possible for T2DM of any duration to be reversed to normal? Second, was the improvement in glucose homeostasis long term or merely a starvation effect that would wane? Our second study, Counterbalance, set out to examine these two questions.

The previous email reports from people with T2DM were confirmed: T2DM was most reversible if the duration of diabetes

was short.⁸ In those less than four years from diagnosis, 85% returned to normal compared with 50% of those with greater than eight year duration. These observations have since been expanded by personal reports. It is clear that some individuals retain the ability to return completely to normal despite two decades or more of T2DM.

In the Counterbalance study a six-month period of weight maintenance followed the weight loss phase. There was no weight gain despite only monthly follow-up, and glucose control remained unchanged. The dramatic improvement in beta cell function was fully retained. This accords with the freedom from diabetes during follow-up periods of many years observed in personal patients. Notions of inevitable beta cell decline are unfounded, provided that beta cells remain relieved of the metabolic stress of excess fat.

Reversal and remission

The term 'reversal' was used in the Counterpoint study in respect of reversing the direction of the twin cycles originally hypothesised. It neatly describes the reversal of the pathophysiological mechanisms underlying the return to non-diabetic glucose homeostasis and is the necessary first step for a person with T2DM who is seeking to return to health. It is a very useful clinical concept. However, following the initial studies, attention needed to expand to the clinical course over time, and this is a separate matter. Remission is the appropriate term for this; it has recently been defined by international consensus.⁹

The tool developed to test the Twin Cycle Hypothesis was more successful in routine clinical use than had been anticipated. But whether or not it was simple enough to be applied in primary care had to be tested. A study of remission was required.

Remission of T2DM in primary care

Could rapid weight loss for remission be used by primary care nurses with appropriate training? They provide the bulk of clinical care for people with T2DM. A larger study was required to test the concept in a randomised clinical trial. Hence, DiRECT (Diabetes Remission Clinical Trial) was set up as a joint project between Newcastle and Glasgow Universities.^{10,11} It was funded as a special project by Diabetes UK. The question was simple, as was the answer - yes.

Remission of T2DM, defined as HbA_{1c} <48mmol/mol for at least six months off all hypoglycaemic drugs, was achieved in 46% of people in the first 12 months. Even at 24 months, 36% were still in remission, off all hypoglycaemic agents despite gradual weight increase. The improvement in overall health and day-to-day wellbeing was documented,¹² as was the cost-effectiveness.¹³

The pressing clinical question now concerns how to avoid future weight regain in the most cost-effective manner. The obvious solution is to change the food environment in simple yet effective ways, such as limiting the amount of sugar added to fast foods and ready meals and preventing deliberate formulation of foods to encourage excess consumption. Governments remain reluctant to act on this, and the question in hand con-

cerns how intensive the follow-up has to be in order to avoid longer-term weight regain.

Interpreting HbA_{1c}

The 'prediabetes' zone of HbA_{1c} is associated with major cardiovascular risks but these are almost entirely a function of the adverse plasma lipid profile. That is not only spinning the twin cycles ever more rapidly but also directly related to atheroma. The slightly raised plasma glucose is not directly causal but rather is an indicator of the very real associated risks.

When the lipid profile is completely normalised, as happens with substantial weight loss, the 10-year risk of cardiovascular events returns completely to normal even if plasma glucose is slightly raised.^{14,15} This point is really important to explain to people who used to have diabetes. They do not have pre-diabetes but rather what might be termed post-diabetes. Their health has indeed been restored. The writing is still on the wall – weight regain will certainly result in metabolic deterioration. Annual follow-up at the very least is required.

Understanding the individual

In the course of all our studies it became clear that weight loss is required to achieve remission irrespective of the initial BMI. In the UK at present, around 50% of people have a BMI under 30kg/m² at the time of diagnosis of T2DM; around 1 in 8 have a normal BMI. How could this be incorporated into clinical thinking? From the Counterpoint, Counterbalance and DiRECT trials it was clear that decreasing BMI from 45 to 42kg/m² produced the same metabolic effects as decreasing it from, say, 27 to 24kg/m². It appeared that too much fat inside the organs, irrespective of BMI, could be responsible for T2DM. The UKPDS dataset was ideal for the purpose of examining the concept. Together with Professor Rury Holman a hypothesis paper was published outlining the 'Personal Fat Hypothesis'.¹⁶ This postulated that once subcutaneous fat capacity for an individual had been exceeded then fat would build up in ectopic sites. Thus, even people regarded as having a normal BMI by population descriptors might accumulate fat in ectopic sites if their safe metabolic depot under the skin was inadequate. Weight loss within the normal range would be expected to bring about remission. The ReTUNE study has been conducted to document the response of people with BMI 21–27kg/m² to stepwise weight loss. Can a personal fat threshold be defined? Preliminary data suggest that once again the answer may be 'yes', and the final results will be available soon.

Although support from a professional is optimal for any individual wishing to achieve remission by dietary weight loss, many people have opted to go solo. The book *Life Without Diabetes* describes how this can be achieved, offering a choice of practical methods (all profits go to Diabetes UK, which has provided the research funding for these studies of aetiology since 2008).¹⁷ "How does the weight loss work, doctor?" is a common question, and this book provides the answer for people with T2DM and for doctors.



Key messages

- T2DM is a condition of simple aetiology, caused by accumulation of more fat than can be tolerated inside the liver and pancreas
- Weight loss of 10-15% will decrease intra-organ fat, restore normal function and non-diabetic glucose control in most people with T2DM duration of up to six years, and in some people with longer duration of diabetes
- A personal fat threshold determines the weight at which an individual develops T2DM, irrespective of BMI

Summary

The problem of what causes T2DM is resolved and the simplicity of the aetiology is clear. If a person exceeds their personal fat threshold, liver fat will increase with increased fat export to the rest of the body. That sets in motion all the problems of ectopic fat and increases cardiovascular risk. Only in those people with beta cells susceptible to fat excess does T2DM develop, and the Twin Cycle Hypothesis explains why. There is a simple bottom line: if a person has T2DM, they have become too heavy for their own body – nothing to do with the population science concept of obesity. The solution is at hand.

Conflict of interest Member of UK government (SACN) working group on low carbohydrate diets and member of advisory board for the NHSE type 2 diabetes remission programme. All opinions in this article are personal. Author of book: *Life without diabetes*. Lecture fees from Novartis, Lilly and Janssen. Research funding from Diabetes UK.

Funding The work would not have been possible without the grant support from Diabetes UK.

Acknowledgements This research journey has been enthusiastically and loyally supported by many people – nurses, dietitians, doctors, scientists and administrators. The contributions of people with T2DM have been invaluable. I am enormously grateful to all.

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