



Understanding the mechanisms of reversal of type 2 diabetes

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Clinical and pathophysiological studies have shown type 2 diabetes to be a condition mainly caused by excess, yet reversible, fat accumulation in the liver and pancreas. Within the liver, excess fat worsens hepatic responsiveness to insulin, leading to increased glucose production. Within the pancreas, the β cell seems to enter a survival mode and fails to function because of the fat-induced metabolic stress. Removal of excess fat from these organs via substantial weight loss can normalise hepatic insulin responsiveness and, in the early years post-diagnosis, is associated with β -cell recovery of acute insulin secretion in many individuals, possibly by redifferentiation. Collectively, these changes can normalise blood glucose levels. Importantly, the primary care-based Diabetes Remission Clinical Trial (DiRECT) showed that 46% of people with type 2 diabetes could achieve remission at 12 months, and 36% at 24 months, mediated by weight loss. This major change in our understanding of the underlying mechanisms of disease permits a reassessment of advice for people with type 2 diabetes.

Introduction

The lifelong nature of both type 1 and type 2 diabetes has always seemed self-evident. In type 2 diabetes, observational studies have documented the gradual worsening of blood glucose control with the need for increasing numbers of antidiabetes drugs.¹ By about 10 years after diagnosis, up to 50% of people require insulin therapy to achieve appropriate blood glucose control. In light of these findings, it is common practice to inform individuals at the time of diagnosis that they have a lifelong condition,² which should be managed as well as possible. The importance of accepting this inevitability has been emphasised.³ The overall result is a learned helplessness on the part of both patients and health-care professionals.

About a decade ago, the importance of liver fat accumulation in determining hepatic insulin resistance became clear^{4,5} and the link with type 2 diabetes was recognised.⁶ Since the degree of sensitivity to insulin determines the effectiveness of regulation of liver glucose production and hence fasting plasma glucose, liver fat content seemed to be a central factor. Observation of the very rapid return to normal fasting plasma glucose in people with type 2 diabetes experiencing sudden food restriction after bariatric surgery⁷ led to the formulation of the twin-cycle hypothesis to explain the potential nutritionally dependent reversal of type 2 diabetes (figure 1).⁹ According to this hypothesis, calorie excess over many years leads to accumulation of fat in the liver, and hence liver insulin resistance. As the liver continuously makes glucose, only restrained by insulin action, the fat-induced liver insulin resistance causes a slight rise in fasting plasma glucose and triggers an increase in insulin production. Because higher insulin levels stimulate conversion of carbohydrate to fat within the liver, a vicious cycle is initiated. Additionally, the excess liver fat is postulated to cause increased export of fat to the whole body, which can be taken up by many tissues, including the pancreatic β cells. Fat is known to decrease acute insulin production, eventually causing

increased post-meal glucose levels. In turn, this process would result in higher insulin levels and a greater tendency to store excess carbohydrate as liver fat. The twin cycles would continue until a point at which the β cells become unable to produce enough insulin to compensate for the resistance to insulin, resulting in diabetes. Importantly, according to the hypothesis, the twin cycles can be reversed if the excess fat load is removed (figure 1).

Previously, it was assumed that the association between bariatric surgery and increased post-prandial glucagon-like peptide-1 (GLP-1) accounted for the rapid restoration of normal fasting plasma glucose; however, this assumption has been shown to be incorrect.^{11,12} A series of studies and trials to test the twin-cycle hypothesis have led to a change in the management of type 2 diabetes in the UK¹³ and the American Diabetes Association now recognises remission as an appropriate aim of management.¹⁴ There has been very clear and positive feedback about the new concept of practical reversal from people with the condition.^{15,16} It is important that the mechanisms underlying the restoration of non-diabetic blood-glucose control are understood by doctors and scientists. In this Personal View, we summarise the studies relevant to the understanding of type 2 diabetes as a reversible clinical state.

Conventional view of type 2 diabetes

The pathophysiology of type 2 diabetes has been regarded as having two distinct components: insulin resistance (ie, tissues losing their ability to respond normally to insulin, leading to hyperinsulinaemia), and a β -cell defect. The insulin clamp is regarded as the gold standard method for assessing insulin resistance, although it mainly assesses muscle with a variable contribution from the liver. Muscle insulin resistance is the earliest detectable feature indicating increased risk of developing type 2 diabetes.¹⁷ The predominant focus of research in the treatment of type 2 diabetes has therefore been to identify

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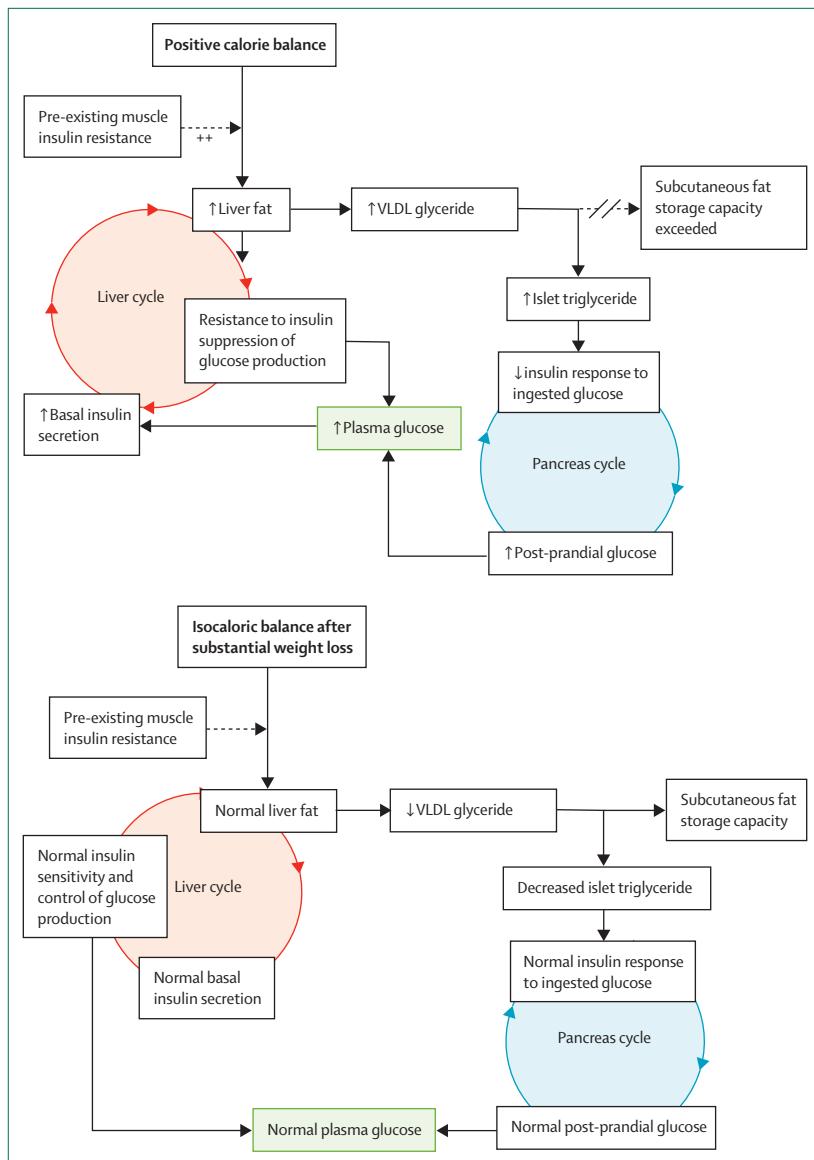


Figure 1: The twin-cycle hypothesis

Upper panel: during chronic positive calorie balance, the de-novo lipogenesis pathway handles carbohydrates which cannot be stored as glycogen, promoting fat accumulation in the liver. Because the process is stimulated by insulin, individuals with a degree of insulin resistance (determined by genetic or lifestyle factors) accumulate liver fat more readily than others due to the higher plasma insulin concentrations. Consequently, the increased liver fat causes resistance to insulin suppression of hepatic glucose production. Over many years, a small increase in fasting plasma glucose leads to increased basal insulin secretion to maintain euglycaemia. The consequent hyperinsulinaemia further increases the conversion of excess calories into liver fat. A vicious cycle of hyperinsulinaemia and blunted suppression of hepatic glucose production is thereby established. Fatty liver leads to increased export of VLDLs triglyceride into the circulation (and thus excess ectopic fat in the blood),⁸ which increases fat delivery to all tissues, including the pancreatic islets. This process is further stimulated by increased plasma glucose concentrations.⁸ Excess fatty acid availability in the pancreatic islets would be expected to impair the acute insulin secretion in response to ingested food, and at a certain level of fatty acid exposure, post-prandial hyperglycaemia supervenes. The hyperglycaemia further increases insulin secretion rates, with consequent increase of hepatic lipogenesis, spinning the liver cycle faster and driving on the pancreas cycle. Eventually the fatty acid and glucose inhibitory effects on the islets reach a trigger level, leading to β -cell failure and a fairly sudden onset of clinical diabetes. Figure based on Taylor (2008)⁹ and adapted from Taylor (2013)¹⁰ and by permission of The American Diabetes Association. Lower panel: removal of excess intra-organ triglyceride and restoration of calorie balance permits return of glucose homeostasis.

better ways of improving muscle insulin resistance with drugs (eg, glitazones) or with diet and exercise.

β -cell dysfunction has proved less amenable to therapy. Data from the United Kingdom Prospective Diabetes Study showed that, at the time of diagnosis, β -cell function, albeit estimated by surrogate indices, had already declined to about 50% of normal,¹⁸ and continues to decline linearly irrespective of pharmacological treatments.¹⁹ Histological studies suggest a roughly 50% decrease in β -cell number in type 2 diabetes and continued loss of β cells, possibly due to apoptosis.^{20,21} On the basis of such evidence, it has been widely accepted that ongoing death or apoptosis of β cells plays a major part in the onset and progression of human type 2 diabetes, although direct evidence is absent.

Evidence for the role of the liver

Over a decade ago, we showed that plasma levels of the liver enzyme alanine aminotransferase (ALT) and triglyceride increase steadily during the 18 months before diagnosis of type 2 diabetes.²² This finding resonated with clinicians who had puzzled over increased plasma ALT and γ -glutamyltransferase concentrations in many people with type 2 diabetes. Because hepatic steatosis is now the most common cause of moderately raised ALT concentrations, the question of liver fat levels in type 2 diabetes has been recognised as important. Findings from several studies have shown the association between hepatic sensitivity to insulin and extent of fat storage in the liver.^{5,23,24}

The continuous production of glucose is one of the most important roles of the liver and is regulated by insulin. The effect of a low-calorie diet on liver fat, hepatic glucose production, and hence fasting plasma glucose has been known for some time (figure 2).^{29,30} Liver fat accumulation has a major effect on the control of plasma glucose concentrations via changes in insulin sensitivity.^{5,31,32} This effect is especially notable in the fasted state (figure 1). Overall, it seems that the increasing ALT concentrations seen before the diagnosis of type 2 diabetes²² reflect increasing hepatic fat accumulation and gradually increasing hepatic insulin resistance.

At about the same time as the recognition of the rise in ALT before the onset of hyperglycaemia, the rapid normalisation of fasting plasma glucose after bariatric surgery was recognised.⁷ Although it had been known for more than 50 years that bariatric surgery could eventually result in remission of type 2 diabetes, the time course of change had not previously been observed. In a 2006 bariatric surgery study in women,⁷ the average participant bodyweight was 152 kg, and it was calculated that they would require about 2700 calories per day to meet their basal energy requirements. But on the evening before bariatric surgery, a severe restriction of calorie intake was instigated (nil by mouth for approximately 24 h then intravenous feeding intended to provide 1800 kcal per day). This restriction is relevant because a year earlier,

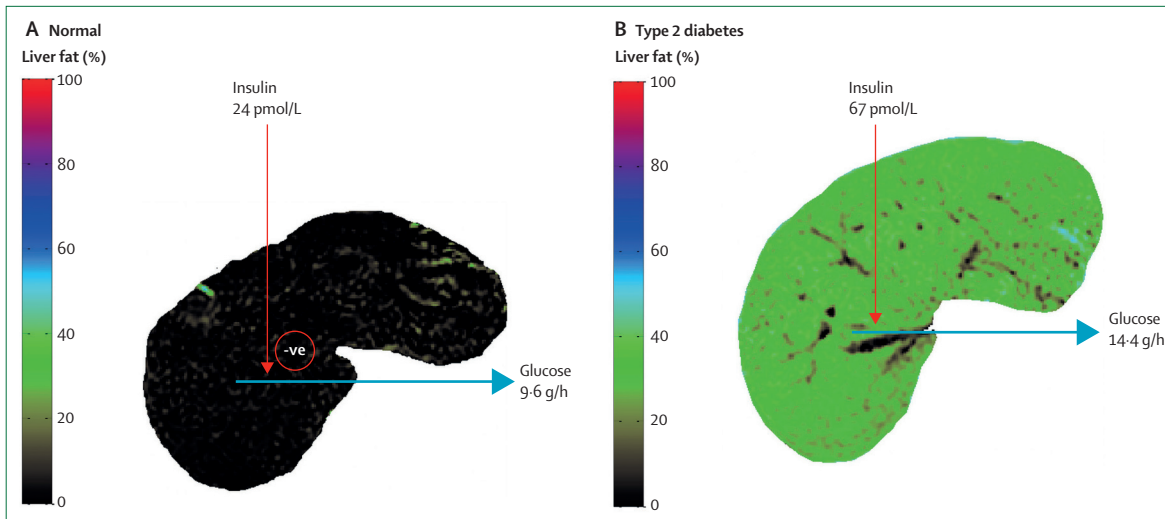


Figure 2: MRI scans of liver colour coded for liver fat, showing regulation of liver glucose output in healthy and in type 2 diabetes

(A) In healthy individuals with low liver fat content, insulin sensitivity of the liver is normal and the low plasma insulin concentration, typical of the overnight fasting state, is able to regulate liver glucose output and therefore keep circulating concentrations normal. Based on data from Taylor et al (1996).²⁵ (B) In patients with type 2 diabetes, liver fat content is typically high,^{26,27} with consequent resistance to insulin action. Although fasting plasma insulin concentrations are increased, these levels are unable to restrain liver glucose output adequately and circulating levels can rise into the diabetic range. Based on data from Singhal et al (2002).²⁸

Petersen and colleagues⁵ had shown rapidly decreasing levels of liver fat and complete normalisation of hepatic insulin sensitivity following calorie restriction (to 1200 kcal per day) in people with type 2 diabetes. This effect could account for the mechanism behind the rapid fall in fasting plasma glucose after bariatric surgery. Indeed, rapid glycaemic normalisation by diet alone was directly observed many years earlier by Walter Pories, often referred to as the father of bariatric surgery, following an abandoned bariatric surgery procedure after which the usual post-operative food restriction was still applied.³³ The 2006 bariatric surgery paper⁷ postulated instead that this beneficial glycaemic effect was mediated by increased post-meal GLP-1 secretion. However, because GLP-1 has negligible glucose effects in the fasting state and no enteral feeding had preceded the observation of normalised fasting plasma glucose, the concept that a post-meal spike in GLP-1 concentration could account for the improvement after bariatric surgery is physiologically improbable. Others have since shown GLP-1 changes post-surgery to be an association, but not a cause, of early glycaemia changes after surgery.^{11,12} The role of oxidative capacity of the liver in enhancing liver fat accumulation and the roles of diacylglycerol and ceramide in the fat-induced hepatic insulin resistance (at least in rodent studies) have now been demonstrated.^{34–37}

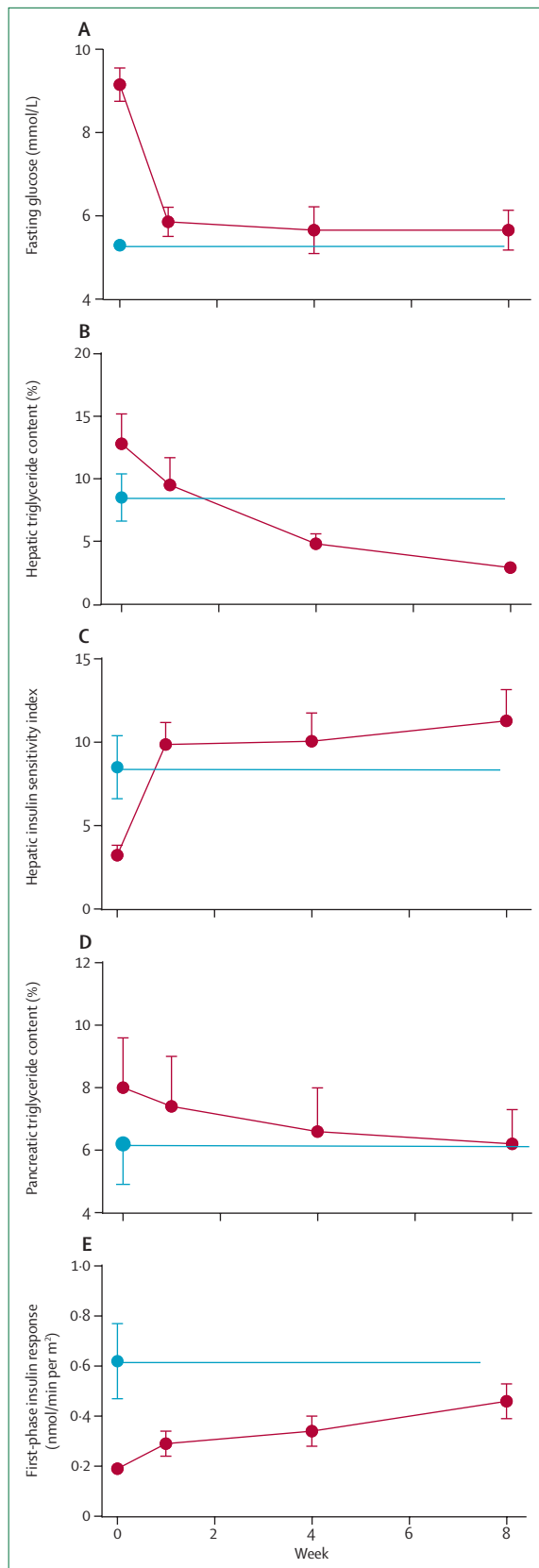
Evidence for the role of the pancreas

Although the new understanding of the role of liver fat in control of hepatic glucose production permitted better understanding of observed changes in fasting plasma glucose after calorie restriction, the inadequate pancreatic insulin secretion characteristic of type 2 diabetes still had to be explained. Data from animal studies offered a

potential explanation because in vitro chronic exposure of β cells to triglyceride or fatty acids decreases their ability to respond to an acute increase in glucose levels.³⁸ The concept that fat could impair β -cell function was not new.^{33,34} Early studies by Clark and colleagues^{41,42} showed the ultrastructural intracellular damage in rodent β cells and insulin-secreting cell lines caused by fairly low concentrations of saturated fatty acids; this endoplasmic reticulum stress has since been recognised in in-vivo studies of type 2 diabetes.^{43,44} Data from rodent studies suggest that the addition of hyperglycaemia is likely to compound the fat-initiated metabolic insult.⁴⁵

If β -cell dysfunction and hepatic insulin resistance shared the common cause of long-term excess fat exposure, the known pieces of the jigsaw could begin to fit together (figure 1). The twin cycle hypothesis was an attempt to put these concepts into a testable form.⁹ It postulates that long-term calorie excess would initiate a self-reinforcing accumulation of liver fat and increase the output of VLDL-triglyceride from the liver (leading to excess ectopic blood fat levels—ie, accumulation in a site not able to provide safe storage of fat). This increased output would in turn contribute to accumulation of ectopic fat, including in the pancreas, leading to impaired β -cell function and eventually to the loss of plasma glucose control and type 2 diabetes. Individuals clearly differ in susceptibility to the deleterious effects of increased intra-organ fat accumulation. Importantly, the hypothesis predicted that if the main driver of the twin cycles could be reversed, via negative calorie balance, then type 2 diabetes could resolve in some, perhaps many, individuals.

Fat within the pancreas is contained in scattered adipocytes, giving a high background level (not relevant



to local metabolic function), and within the cytoplasm of both exocrine and endocrine cells. It is important that quantification excludes the fibro-fatty tissue between lobules; precise quantification using advanced magnetic resonance methods is possible.^{46,47} Pancreas fat content varies widely between individuals⁴⁷⁻⁴⁹ and sequential measurement is required to examine metabolic effect.^{26,27,50,51} It is increased in patients with type 2 diabetes^{48,26,52,53} and importantly does not decrease with weight loss over 8 weeks unless type 2 diabetes is present.⁵¹ Data suggest that there is a small but metabolically significant pool of excess triglyceride within both endocrine and exocrine cells of the pancreas in people with type 2 diabetes.

Testing the new hypothesis

The twin-cycle hypothesis could be tested most simply by observing what happens in response to sudden calorie restriction in people with type 2 diabetes. If the hypothesis was correct, the body would have to use its supplies of stored energy, and there would be two main results. First, fat stored within the liver would be utilised and both hepatic insulin resistance and fasting plasma glucose would fall. Second, pancreas fat content would decrease and glucose-induced insulin secretion would normalise. To test the hypothesis, a precise method of measuring pancreas fat in vivo was developed and a robust, practicable means of decreasing calorie intake was devised as part of a clinical mechanistic study.⁴⁴ The Counterpoint (COUNTERacting Pancreatic inhibitiON of INsulin secretion by Triglyceride) study²⁶ was successful in achieving a 15.3 kg weight loss over the planned 8-week period in a typical group of people (n=11) with type 2 diabetes.

As observed during the period of calorie restriction around bariatric surgery, fasting plasma glucose normalised within 7 days of instituting sudden negative calorie balance in Counterpoint, even though metformin was withdrawn on day 1 of the diet. Liver fat levels and hepatic insulin sensitivity also normalised over the same time course, returning to levels seen in weight-matched non-diabetic control participants (n=8) within the 7 days (figure 3).

During the study, pancreas fat content decreased and the first-phase insulin response gradually increased and had normalised by week 8. These findings were paradigm shifting because it was previously believed that restoration of normal first-phase insulin secretion could

Figure 3: Results of the Counterpoint study

Sequential changes over 8 weeks after withdrawal of metformin therapy and initiation of a very-low-energy diet (600 kcal per day) in people with type 2 diabetes (red) and matched non-diabetic controls studied at a single timepoint (blue). Figure shows changes in (A) fasting plasma glucose, (B) hepatic triglyceride content, (C) hepatic insulin sensitivity index, (D) pancreatic triglyceride content, and (E) first-phase insulin response to a 3 mmol/L increase in plasma glucose concentration. Figure adapted from Lim et al (2011).²⁶

	Evidence for liver and pancreatic fat as key drivers of type 2 diabetes	Evidence for the reversibility of liver and pancreatic fat and diabetes remission with intensive weight loss
Bodyweight	Weight gain is the strongest modifiable risk factor for patients with type 2 diabetes ³⁹	Intensive weight loss by any method can reverse type 2 diabetes, including in some taking insulin therapy ^{46,54,55}
Liver enzymes	Higher plasma ALT and GGT concentrations, as modest proxies for excess liver fat, are common before patients develop diabetes; ALT levels also rise during short-term conversion to type 2 diabetes ²⁷	Plasma ALT and GGT concentrations decline in parallel with weight loss and glucose reduction ^{46,27,56}
Liver fat	Hepatic fat levels are excessive in at least 70% of patients with type 2 diabetes ²⁷	Fatty liver prevalence normalises rapidly with intense weight loss in patients with diabetes ^{12,26,51}
Liver insulin sensitivity	Higher liver fat is associated with impaired hepatic insulin sensitivity ^{24,31,32}	Hepatic insulin sensitivity normalises rapidly with intensive weight loss via calorie restriction ^{26,27,50,54}
Relation between liver fat and liver insulin sensitivity	High fatty acids levels in hepatocytes disrupt insulin-mediated suppression of hepatic glucose production ⁵⁸	Rapid return to normal hepatic insulin sensitivity during negative calorie balance ^{53,6,50}
Pancreas fat	Pancreatic fat levels are increased in people with β -cell dysfunction and type 2 diabetes ^{46,53,59}	Pancreatic fat declines gradually with intensive weight loss only in people with diabetes ⁵¹
β -cell function	First-phase insulin response impaired in patients with type 2 diabetes	First-phase insulin response returns following substantial weight loss ^{26,27,50}
Relation between pancreas fat and β -cell function	Excess fatty acids known to bring about β -cell dedifferentiation and inhibit insulin release ^{41,42,60}	Evidence for β -cell recovery with weight loss and return of insulin production capacity ^{6,27,50}
Change in bodyweight	Weight regain after intensive weight loss is linked to rapid re-emergence of excess liver fat and glucose increases ²⁷	Sustained weight loss associated with sustained liver and pancreatic fat reductions and sustained glycaemia benefits ^{27,50}

ALT=alanine aminotransferase. GGT= γ -glutamyltransferase.

Table 1: Key observational and treatment-based evidence that supports the twin-cycle hypothesis of the cause of type 2 diabetes

not be achieved in people with type 2 diabetes (figure 3). The predictions of the twin-cycle hypothesis had therefore been confirmed (table 1).

Because commencement of exercise programmes can induce compensatory eating,^{61–63} thus limiting weight loss, a diet-only approach was taken to achieve the necessary 15 kg average weight loss in Counterpoint and subsequent studies. However, a sustained increase in daily physical exercise can be a very important component of long-term avoidance of weight regain.⁶⁴

Durability of the reversal of type 2 diabetes after the return to normal eating

To show durability (and therefore wider clinical applicability) of the return to non-diabetic plasma glucose levels, a nutritional and behavioural approach to achieving long-term isocaloric eating after the acute weight loss phase was required. The Counterbalance (COUNTERacting BetA cell failure by Long term Action to Normalize Calorie intake) study⁵⁰ (<4 years duration group: n=15; >8 years duration group: n=14) involved rapid weight loss, stepped food reintroduction over 2 weeks then 6 months of follow-up by specialist staff in a research centre. A liquid diet replacement was used to induce weight loss, followed by stepped reintroduction of normal foods, and then supportive follow-up with an emphasis on portion size and regular checks of bodyweight. No significant weight regain occurred; on the contrary, the group lost roughly 14 kg bodyweight and maintained post-weight loss normalisation of blood glucose control. The overall remission rate (HbA_{1c} <6.5% [48 mmol/mol] on two occasions, at least 2 months

apart)⁶⁵ remained constant (60% in the short duration group and 21% in the long duration group) over the 6 months of follow-up.

These findings were extended in the DiRECT (Diabetes Remission Clinical Trial),^{66,67} which was done entirely in primary care. DiRECT was much larger than the Counterpoint and Counterbalance studies (n=149 in both intervention and control groups) and involved participants who had type 2 diabetes for up to 6 years. The mean weight loss in the intervention group at 12 months was 10 kg (analysed on an intention-to-treat basis). At 12 months, diabetes remission was achieved in 68 (46%) of 149, and 53 (36%) of 149 at 24 months in the intervention group, off all antidiabetes drugs. In both the Counterbalance study and in DiRECT, people who had reversed their type 2 diabetes after weight loss remained free of diabetes if they avoided subsequent weight regain. The details and results of the Counterpoint, Counterbalance, and DiRECT studies are summarised in table 2.

Some longer-term data are available from the Look AHEAD study,⁶² in which mean weight loss was greater in the intensive lifestyle group compared with the control group receiving standard management by 3.9% after 4 years of follow-up, and was associated with 5.3% more participants undergoing remission of type 2 diabetes. In Look AHEAD, the focus was not only on diet but also on intensive exercise programmes from the outset, which are not easily sustained, and therefore could have led to greater weight regain. Notably, the Look AHEAD study population was different from the DiRECT population in important ways: in Look AHEAD, about a fifth of patients were on insulin at the start of the study, median duration

	Counterpoint ²⁶	Counterbalance ⁵⁰	DiRECT substudy ²⁷
Description	Reversal in people diagnosed with type 2 diabetes for less than 4 years	6 months sustained reversal in people diagnosed with type 2 diabetes for up to 23 years	12 months sustained reversal by primary care intervention in people diagnosed with type 2 diabetes for up to 6 years
Number of participants	11	29	64
Duration of diabetes (years)	0–4	0–23	0–6
Previous treatment	Diet with or without metformin	Any oral drugs apart from thiazolidinediones	Any drugs apart from insulin
Weight loss (kg)	15.3 (SE 1.2) (all responders)	Responders: 15.8 (SE 0.5); non-responders: 13.6 (SE 0.7)	Responders: 16.2 (SE 1.2); non-responders: 13.4 (SE 1.4)
Timing of observations after weight loss	Immediately after weight loss	2 weeks, then 6 months, after weight loss	2–4 weeks, then 7–8 months, after weight loss
HbA _{1c}	Baseline: 7.4% (SE 0.3) (57 [SE 3] mmol/mol); after weight loss: 6.0 (SE 0.2) (42 [SE 2] mmol/mol)	Responders baseline: 7.1% (SE 0.3) (55 [SE 4] mmol/mol); responders after weight loss: 5.9% (SE 0.2) (41 [SE 2] mmol/mol); non-responders baseline: 8.4% (SE 0.3) (68 [SE 3] mmol/mol); non-responders after weight loss: 7.8% (SE 0.3) (62 [SE 3] mmol/mol)	Responders baseline: 7.4% (SE 0.2) (57 [SE 2] mmol/mol); responders after weight loss: 5.8% (SE 0.1) (40 [SE 1] mmol/mol); non-responders baseline: 7.9% (SE 0.2) (63 [SE 2] mmol/mol); non-responders after weight loss: 7.6% (SE 0.2) (90 [SE 2] mmol/mol)
Number (%) that achieved non-diabetic status*	11/11 (100%)	13/30 (43%)	29/45 (64%)
Data for the DiRECT substudy are currently available only up to 12 months of follow-up. *Non-diabetic status defined as HbA _{1c} <6.1% (42 mmol/L) and fasting plasma glucose <6.1 mmol/L (110 mg/dL).			

Table 2: Comparative data from pathophysiological studies of type 2 diabetes reversal

of diabetes was longer (5 years compared with 3 years in DiRECT), and many participants had diabetes for more than 10 years. The ethnic mix was also quite different, with only about 60% being white in Look AHEAD, whereas this figure was close to 100% in DiRECT. As such, these two trials are not easily comparable.

Many individuals continue to have a BMI over 30 kg/m² after achieving remission of type 2 diabetes, the implications of which need to be considered. After the acute weight loss, mean BMI was 28.6 kg/m² in the Counterbalance study and 31.5 kg/m² in the DiRECT study, and hence about half of each group remained obese. An important question therefore was whether the remaining excess fat might redistribute into the liver and pancreas when isocaloric eating resumed. Baseline mean liver fat content was 12.8% in Counterbalance and 16.0% in DiRECT. In Counterbalance, weight loss was associated with a fall in liver fat to 2% (low normal) in those who reversed their diabetes, and this level was unchanged after 6 months follow up. In the DiRECT study responders, liver fat content fell to 3.3% after rapid weight loss and a return to isocaloric eating (5 months) then to 3.0% at 12 months (figure 4). It seems that if total body fat burden falls below an individual threshold, and this fall is sustained, then ectopic fat does not reaccumulate. This finding is consonant with the personal fat threshold concept,⁶⁹ which is supported by genetic data linking limited capacity for subcutaneous fat storage with cardio-metabolic disease,⁷⁰ and suggests that BMI is only a very general guide to a healthy metabolic weight for an

individual. A parallel pattern of change was observed for pancreatic fat. Self-reported observations, although open to bias, suggest that individuals who lost substantial weight via dietary change remained free of diabetes over several years if weight regain was avoided.^{70,71}

Can type 2 diabetes of any duration be reversed?

The Counterpoint study involved people with type 2 diabetes up to 4 years after diagnosis. However, it was necessary to find out the effect of a longer duration of diabetes on reversibility; therefore, the subsequent Counterbalance study⁵⁰ involved people that had been diagnosed with type 2 diabetes for 0.5–23 years. All 29 participants showed an improvement in fasting plasma glucose by the end of the first week of the study.⁵⁰ 13 (87%) of 15 of people who had been diagnosed with diabetes for less than 4 years achieved non-diabetic concentration of fasting plasma glucose (<7 mmol/L). The mean fasting plasma glucose after 6 months in the subgroup that had been diagnosed for less than 4 years was 5.8 (SE 0.2) mmol/L; for those diagnosed for 8–12 years, it was 6.2 (SE 0.7) mmol/L, and for those diagnosed for 12 years or more was 10.6 (SE 1.7) mmol/L. No patients who had been diagnosed with diabetes for more than 11 years returned to non-diabetic fasting plasma glucose concentrations. Loss of the specialised β-cell phenotype (dedifferentiation) is probably a crucial mechanism that underlies the conversion to type 2 diabetes in susceptible individuals.^{72–76} Markers of dedifferentiation are expressed in β cells from pancreases of people with type 2 diabetes.^{77–79} Not everyone agrees that dedifferentiation is the sole

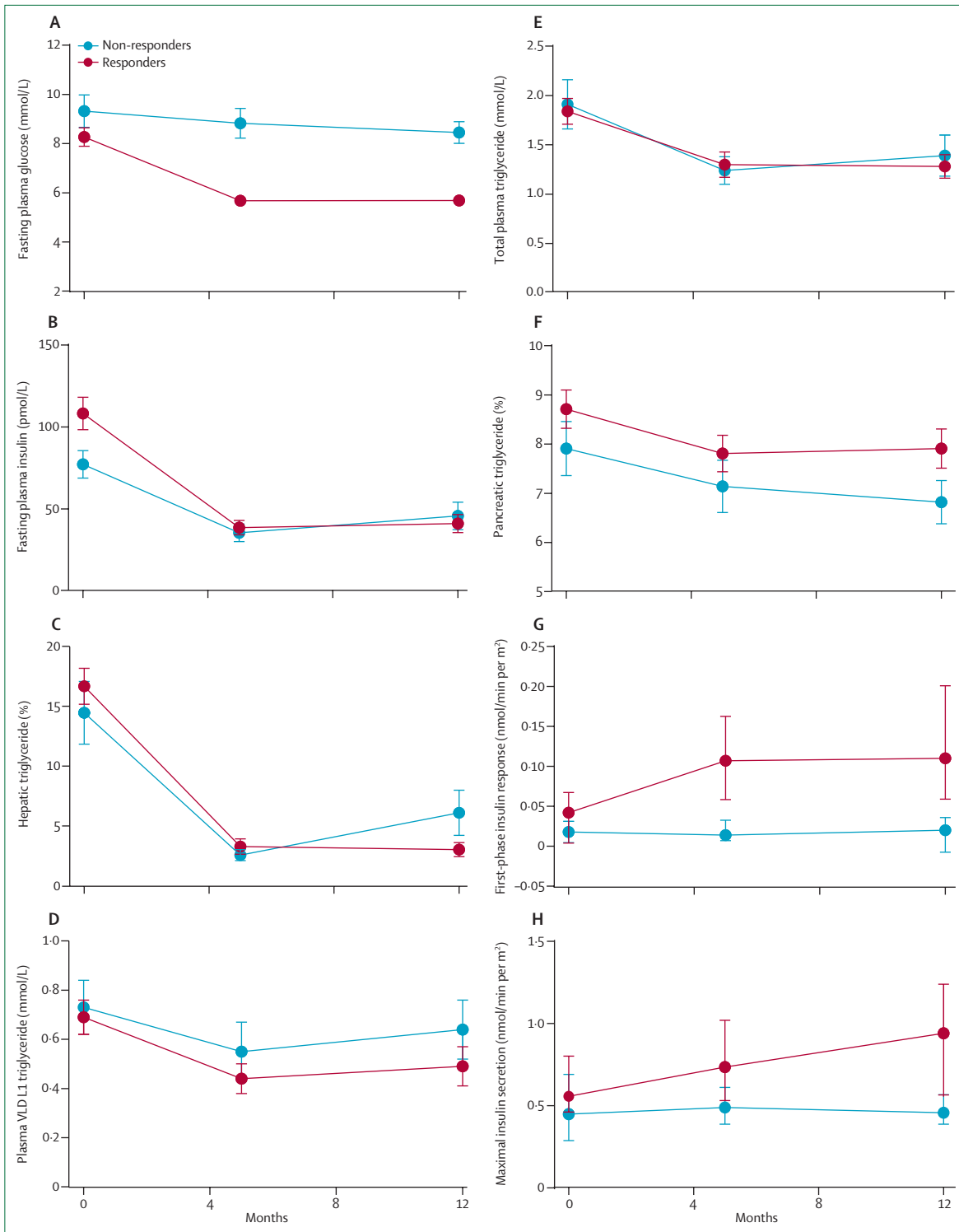


Figure 4: Results of the DiRECT mechanistic studies

Sequential changes over 12 months after withdrawal of antidiabetes drugs and initiation of a low-energy diet (825–853 kcal per day) in people with type 2 diabetes. Figure shows changes in (A) mean fasting plasma glucose concentration, (B) mean fasting plasma insulin concentration, (C) mean hepatic triglyceride content, (D) mean VLDL1-plasma triglyceride concentration, (E) mean total plasma triglyceride content, (F) mean pancreatic triglyceride content, (G) median first-phase insulin response to intravenous glucose stimulation, and (H) median maximal insulin secretion in response to arginine. Error bars for mean values are SE and for median values are IQR. Figure adapted from Taylor et al (2018),²⁷ by permission of Elsevier.

process underlying β -cell dysfunction in type 2 diabetes, but if this state persists too long in an individual it could result in irreversible loss of endocrine function results. It is now possible to incorporate the histological and cell biological processes with observations during clinical reversal of the disease process.⁸⁰ The histological observation of substantially lower β -cell numbers seems likely to relate to the insulin immunostain, such that β cells that had stopped producing insulin were simply not identified, and incorrectly considered to be non-viable rather than non-functional.

Differences between prediabetes and post-diabetes

Although many people who achieve and maintain substantial weight loss return to a state of normal glucose metabolism, others achieve an HbA_{1c} that is non-diabetic (<48 mmol/mol), but not in the normal range. However, the parallel blood pressure and lipids improvements show that these individuals have substantially improved their overall likelihood of long-term good health. The Counterbalance study group were supervised to avoid weight regain during 6 months follow up, and mean blood pressure and lipids improved substantially.⁵⁰ The 10-year cardiovascular risk assessed by the QRISK score⁸¹ fell on average from 23% to 7% for those that achieved remission in this closely supervised study. In this group, in which the average participant age was 55 years, calculated heart age fell from 71 to 56 years. In DiRECT, the recorded Serious Adverse Events were substantially lower in the second year. This was driven mainly by lower numbers of major vascular events and cancers although numbers were too small to show statistical significance within each category.⁶⁷ In the Swedish Obese Subjects study, bariatric surgery-induced weight loss brought a 32% lower risk for macrovascular complications compared with the control group over a 15 year follow-up period.⁸² Together these findings suggest that major health gains are a consequence of weight gain avoidance.

A term is now required to describe people who have achieved stable weight with normalised intrahepatic and intrapancreatic fat and reversed their type 2 diabetes. Roughly two-thirds of those in remission in the DiRECT study achieved normal fasting plasma glucose and HbA_{1c}. For the third who remained below the diabetic range but not in the normal range, it would be inappropriate to describe these individuals as having prediabetes, as this state is associated with cardiovascular risk (related mainly to the associated dyslipidaemia). It has been proposed that their metabolic state would most appropriately be termed post diabetes, retaining the implication that they remain susceptible to diabetes if weight regain occurs.¹⁶ Return to previous weight seems to be uniformly associated with return of diabetes as assessed both by informal observation of former research participants, and from the 24 month data of DiRECT.⁶⁷ In the latter trial, participants who had been in remission at

12 months but reverted to the diabetic state at 24 months had regained 7.1 (SD 5.4) kg over this time interval.⁶⁷ People in the post-diabetes state do not have diabetes, and this is important not only for insurance purposes but also as a motivating factor to avoid weight regain. Ongoing support for people with post-diabetes is essential because sufficient weight regain will increase the likelihood of diabetes returning. In UK primary care, such individuals would appropriately be assigned Reid code C10P, indicating resolution of diabetes but the need for ongoing annual checks.⁶⁵

Microvascular complications are very unlikely to occur or advance in the post-diabetes state, as observed after pancreas transplantation in type 1 diabetes or after bariatric surgery-induced remission of type 2 diabetes.^{82,83} However, if moderately severe retinopathy is present then there is a risk of worsening to treatable maculopathy or proliferative retinopathy following the sudden fall in plasma glucose concentrations.^{84,85} Retinal imaging within 4–6 months should be required for individuals in the post-diabetes state with more than minimal retinopathy.

Future questions

Calorie restriction to achieve substantial weight loss and remission of type 2 diabetes has previously been observed,^{30,86} raising the question of how best to maintain the initial advantage provided by a low-calorie liquid diet. Recent national dietary guidelines have emphasised the need to provide individualised advice, rather than only one dietary prescription for everyone, and high quality studies in primary care are needed to assess the dietary advice and the nature of the behavioural support provided to maintain remission of type 2 diabetes.

Genetic traits seem likely to underlie the varying susceptibility of individuals to fat-induced β -cell dedifferentiation, in view of the fact that 72% of people with a BMI greater than 40 kg/m² do not have diabetes.⁸⁷ These traits are likely to operate via both capacity for safe, subcutaneous storage of fat and β -cell susceptibility. Large numbers of people with type 2 diabetes have a normal BMI (<25 kg/m²): 16% of those aged over 55 years and 10% of those aged 16–54 years.⁸⁸ Notably, all of the studies on reversing type 2 diabetes have involved people with a BMI greater than 27 kg/m²; therefore it is not known whether people with type 2 diabetes and a normal BMI can also undergo type 2 diabetes reversal via calorie-restriction-induced weight loss. In this group, it is likely that is an increased proportion of people who have been misdiagnosed and actually have maturity onset diabetes of the young or slow-onset type 1 diabetes. There could also be unrecognised diagnostic categories, although the concept that type 2 diabetes itself has more than one cause seems unlikely.

The β -cell factors that prevent return to normal plasma glucose control need to be identified, because weight loss of more than 15 kg did not reverse type 2 diabetes in five (14%) of 36 individuals diagnosed with type 2 diabetes for

up to 6 years in the DiRECT study.²⁷ Similarly, weight loss of more than 25 kg after bariatric surgery did not cause remission of diabetes in 13 (39%) of 33 individuals diagnosed with type 2 diabetes for an average of 10 years.⁸⁹ In DiRECT, 5 (14%) of 36 people who lost 15 kg or more did not achieve remission compared with 37 (66%) of 56 of those who only achieved a 5–10 kg weight loss.⁶⁶ Duration of diabetes seems to be the major determining factor^{90,91} and weight loss above 20 kg is not progressively associated with higher rates of remission.⁹¹

Many people who develop type 2 diabetes at younger ages (ie, aged 35 years or younger) have much higher bodyweights than those diagnosed much later in life.⁸⁹ Whether such individuals need to lose more than 10 kg to reverse their type 2 diabetes is also an important and testable question.

Studies on mechanisms of reversal of type 2 diabetes have so far involved individuals almost entirely of white European ethnic backgrounds and further work is now urgently needed in other populations (eg, south Asian, Chinese, and black ethnic groups), which are more susceptible to diabetes at lower average BMIs compared with white Europeans. Whether such individuals need to lose less weight than white people to reverse their diabetes can also be investigated. Such work would be very appropriate because of the rapidly rising prevalence of type 2 diabetes worldwide, particularly in south Asia and in low-income and middle-income countries in general, where the consequent burden on individuals and health-care systems are profound.⁹² Such work could be particularly helpful in areas where current access to diabetes drugs is scarce.

Finally, a joint consensus statement from the Association of British Clinical Diabetologists and the Primary care Diabetes Society has defined remission of diabetes as HbA_{1c} <48 mmol/mol (<6.5%) on two occasions at least 6 months apart, off all anti-diabetic agents.⁹³ This definition uses the boundary internationally defined for the onset of type 2 diabetes. The utility of the time interval to show that type 2 diabetes is no longer present requires to be assessed in future studies.

Conclusion

Type 2 diabetes is a condition that develops in people who consume more calories than they require over a long period of time. More fat than the individual's body can safely store accumulates, leading to excess liver and pancreatic fat and subsequent loss of plasma glucose control. Susceptibility to fat excess seems to vary considerably between individuals. In the early years after diabetes onset, removal of the excess fat in the liver and pancreas via intensive but achievable weight loss can in many cases lead to normalisation of hepatic glucose production and possible β -cell redifferentiation, and diabetes can be reversed. As physicians, we must grasp this paradigm shift in our understanding of type 2 diabetes for the benefit of our patients.

Search strategy and selection criteria

We systematically searched PubMed for English-language articles published between Jan 1, 1960, and Oct 15, 2018. Our search terms included "type 2 diabetes", "pathogenesis", and "remission". We assessed articles by title and abstract to identify relevant studies. Studies were also sought from within reference lists of eligible publications. Studies and trials that assessed the reversibility or remission of type 2 diabetes and explored relevant mechanisms were considered relevant to the topic of the Personal View.

Contributors

AAM contributed lipoprotein concepts and NS helped to develop concepts relevant to diabetes pathogenesis. RT conceived the initial hypothesis and drafted the Personal View. All authors contributed to the analysis of published data and interpretation of findings. All authors reviewed and revised the Personal View and read and approved the final submitted version.

Declaration of interests

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