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Calorie restriction and reversal of Type 2 diabetes

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Abstract

Introduction. Type 2 diabetes a major global health problems and has been believed to be a lifelong condition with inevitable worsening. Steadily increasing numbers of drugs appeared to be required to achieve even modest control. Early type 2 diabetes has now been shown to be reversed by substantial weight loss and this has allowed temporal tracking of the underlying pathophysiological changes.

Areas covered. In early type 2 diabetes, negative calorie balance decreases liver fat within days, and allows return of normal control of hepatic glucose production. Over 8 weeks, the negative calorie balance allows raised levels of intra-pancreatic fat and simultaneously first phase insulin secretion to normalise. These findings are consistent with the 2008 Twin Cycle Hypothesis of the aetiology and pathogenesis of type 2 diabetes. Individuals develop type 2 diabetes when they exceed their personal fat threshold for safe storage of fat and there is no difference in pathophysiology between those with BMI above or below 30 kg/m^2.

Expert Commentary. Type 2 diabetes can now be understood as a state of excess fat in liver and pancreas, and remains reversible for at least 10 years in most individuals.

1. Introduction

The pathogenesis of type 2 diabetes has been regarded as involving two separate processes bringing about insulin resistance and relative beta cell failure [1-3]. However, the rapid changes in population prevalence of the condition depending upon food surplus or shortage [4, 5] suggests either that both processes are affected by nutrient supply or that a single pathway is involved. By tracking the pathophysiological changes which occur during the transition from type 2 diabetes back to normal metabolic control it has been possible to test the predictions of the 2008 Twin Cycle Hypothesis [6]. This review discusses these findings in relation to established knowledge.

2. Contribution of the individual metabolic organs to type 2 diabetes

2.1. Liver

Inside the liver, all triglyceride is stored inside hepatocytes. The sensitivity of the liver to insulin is strongly related to the triglyceride content [7]. As fasting glucose concentration is principally determined by the rate of glucose production from the liver, improving insulin sensitivity of the liver decreases fasting plasma glucose [8, 9].

Excess accumulation of liver fat occurs when the total daily calorie intake exceeds expenditure day after day, and year after year. If more calories are ingested than metabolised in any 24 hour period then: a) any excess fat is stored subcutaneously, in visceral fat or in the liver; b) any excess carbohydrate cannot be stored as such once the glycogen depots are full and it has to be turned into fat by *de novo* lipogenesis. This process only happens in the liver in humans, and triglyceride synthesised by this route is particularly likely to be stored in hepatocytes rather than transported for storage in subcutaneous adipose tissue where it is metabolically inert. As *de novo* lipogenesis is stimulated by insulin, those people who are relatively insulin resistant in muscle - and who therefore have a raised plasma insulin level - are especially likely to accumulate fat in the liver. This could explain the reason why muscle insulin resistance is a very early signal of risk for type 2 diabetes [2, 10].

The practical application of this was elegantly shown by overfeeding sucrose to overweight volunteers for three weeks. The result was a sharp increase in liver triglyceride content [11]. This was associated with a 30% rise in serum ALT, reflecting the associated metabolic stress on the hepatocytes. A larger scale demonstration of the end result of this process was achieved by Sattar and colleagues [12]. During the 15 year follow up of the West of Scotland Coronary Prevention Study group of 6595 men, some developed diabetes. Stored plasma samples were analysed to allow retrospective reconstruction of the pattern of change in liver enzymes in those who were about to develop diabetes compared with the majority who did not develop diabetes. The diagnosis of type 2 diabetes was preceded by a steady rise in serum ALT over at least 18 months. As the mean level was well within the normal range it would be unlikely to be detected in any one individual. Clearly, liver fat builds up during the pre-diabetic phase of type 2 diabetes.

The recent studies of reversal of type 2 diabetes to non-diabetic glucose control show that the first impact of a hypocaloric diet is to decrease liver fat stores. In the Counterpoint study, a diet of 600-800 kcal/day achieved a 30% decrease in liver triglyceride in the first 7 days, bringing it down to the level of weight matched controls [13]. Simultaneously, fasting plasma glucose fell from 9.2 to 5.9mmol/l. A 7 day very low calorie diet was observed to improve fasting plasma glucose with no effect on first phase insulin secretion, and change in hepatic insulin sensitivity was not measured [14]. This effect of sudden negative calorie balance on fasting plasma glucose is seen not only after a purely dietary intervention, but also after the food restriction imposed by bariatric surgery [15].

2.2. Muscle

Lower sensitivity of skeletal muscle to insulin is widely regarded as the earliest feature predicting onset of type 2 diabetes [10]. It prevents muscle from contributing to immediate post-meal storage of glucose as glycogen and hence post-prandial glucose levels rise considerably [16, 17]. However, it is important to recognise that 'insulin resistance' is not a distinct condition but a continuously distributed parameter in any population. The distribution of whole body (largely muscle) insulin sensitivity in type 2 diabetes is entirely within the range of the non-diabetic population but merely towards the lower range [18]. Separation of the distinct contributions of muscle and liver have

shown that early improvement in control of fasting plasma glucose is related only to improvement in liver insulin sensitivity [8, 13]. It has recently been demonstrated that the resumption of normal or near normal diurnal blood glucose control does not require improvement in muscle insulin sensitivity [13, 19]. Although this may at first appear surprising, it is supported by a wide range of earlier observations. Mice totally lacking in skeletal muscle insulin receptors do not develop diabetes [20]. Humans who have the PPP1R3A genetic variant of muscle glycogen synthase cannot store glycogen in muscle after meals but can have normal glucose tolerance [21]. Many normoglycaemic individuals maintain normal blood glucose with a degree of muscle insulin resistance identical to those who develop type 2 diabetes [18].

Examination of individuals at the extremes of the range of insulin sensitivity led to the concept that there might be an underlying primary defect in mitochondrial function in skeletal muscle which predisposed to type 2 diabetes [22]. However, no defect is present in early type 2 diabetes but can be shown to be directly related to ambient plasma glucose concentration [23]. The rates of mitochondrial ATP production can be modified by increasing or decreasing plasma fatty acid concentration [24, 25]. Also, the onset of insulin stimulation of mitochondrial ATP synthesis is slow, gradually increasing over hours and quite distinct from the almost instantaneous onset of insulin's metabolic effects [26]. It appears that there are secondary effects on mitochondrial function of hyperglycaemia and excess fatty acids, but no evidence for a primary mitochondrial defect underlying common type 2 diabetes.

The physiologic importance of muscle insulin resistance is likely to operate over a time period of many years. The presence of longstanding muscle insulin resistance will not of itself cause blood glucose levels to rise but the raised plasma insulin levels will expedite accumulation of liver fat by stimulation of *de novo* lipogenesis [10].

2.3. Beta cell

In vitro study of islets exposed to a sudden increase in fatty acid concentration demonstrates the interaction between glucose and excess fatty acid supply [27]. When islets from ZDF rats genetically predisposed to develop diabetes are exposed to even a low concentration of palmitic acid for 48 hours, the beta cells no longer secrete insulin normally in response to glucose. However, islets from animals not genetically predisposed to glucose can withstand the excess fat supply and retain glucose mediated

insulin secretion [27]. The elegant studies from Clarke's group have extended knowledge about effects of specific fatty acid upon islet and INS-1 cells and have shown it to be reversible [28-30]. The relevance to human islets has been demonstrated in that exposure to a low concentration of saturated fatty acids brings about avid uptake of fat and loss of glucose mediated insulin secretion [31]. These studies demonstrate potential mechanisms, even though the effect of excess supply of fatty acids *in vivo* is more subtle and over very long time periods.

It is particularly noteworthy that diabetes in the ZDF model is completely preventable by restriction of food intake [32]. These observations together illustrate very well the interaction between genetic susceptibility and environmental factors in the aetiology of type 2 diabetes. In the ZDF rat, a rapid increase in pancreatic fat precedes the onset of hyperglycaemia [27]. This is supported by the observations using a precise method of measuring intra-pancreatic fat in people with type 2 diabetes [13, 19]. However, it must be emphasized that the pancreas is typically one third smaller in type 2 diabetes, with highly irregular borders [33] and that if 'off the shelf' programs to determine pancreas fat are used then falsely high values will be obtained due to visceral fat being included as being within the organ, given its highly irregular shape and small volume in type 2 diabetes.

Post-mortem studies appear to show that beta cell number at diagnosis of type 2 diabetes is around 50%, and lower in long duration diabetes [1, 34]. This appears to agree with the finding that beta cell function is decreased to around 50% of normal at the time of diagnosis and decreases thereafter [3]. However, lineage tracing of beta-cells in mice during ageing and multiple pregnancies has shown that apparent loss of beta-cell mass in this animal model of diabetes is due to dedifferentiation rather than cell death [35]. Loss of insulin staining as a consequence of loss of the specialised function to produce insulin was demonstrated in parallel with induction of genes not expressed in normal adult beta-cells. This has now been confirmed in human islets prepared but not used for islet transplantation [36, 37]. Hence, the impression that type 2 diabetes is characterised by irreversible beta cell death has been shown to be flawed in that the beta cells are not 50% dead, but simply not identifiable by insulin immunostaining. Up to a certain point, de-differentiation is reversible allowing full recovery of the

specialised function to produce insulin. The corollary is that the beta cell defect can reasonably be expected to be reversible in vivo at least during the early years of type 2 diabetes.

3. Insight into the potential reversibility of type 2 diabetes

The first hint that type 2 diabetes was a fully reversible syndrome came from bariatric surgery over half a century ago, and drawn to widespread attention by Walter Pories [38]. A randomised prospective study demonstrated the superiority over intensive medical therapy for type 2 diabetes [39]. Remission of diabetes was shown to be related to the degree of weight loss rather than allocation to either group. This was achieved in 73% of the surgical group and 13% of the medical group as surgery was simply more effective in achieving and maintaining weight loss [40]. Type 2 diabetes can be reversed by applying a surgical procedure which diminishes total body fat load.

The normalisation of glucose in type 2 diabetes within days after bariatric surgery, before substantial weight loss [15], led to the widespread belief that surgery itself brought about specific changes mediated via incretin hormone secretion [41, 42]. This reasoning overlooked the major change which follows bariatric surgery: an acute, profound decrease in calorie intake. Typically those undergoing bariatric surgery have a mean body weight around 150 kg [15] and would therefore require daily intake of at least 13·4 MJ/day (3,200 kcal/day) for weight maintenance [43]. It is known that hypocaloric dieting will mobilise fat first from the liver and other ectopic sites and only then from visceral and subcutaneous fat [44]. This process has been studied in detail during more moderate calorie restriction in type 2 diabetes over approximately 8 weeks [8]. Fasting plasma glucose was shown to be improved because of an 81% decrease in liver fat content and normalisation of hepatic insulin sensitivity with no change in the insulin resistance of muscle. The Counterpoint and Counterbalance studies have both shown that more vigorous calorie restriction brings about more rapid fall in liver fat and in fasting plasma glucose [13, 19]. The temporal association is highly suggestive of a causal relationship. If this is maintained then intra-pancreatic fat levels fall and in step with this, insulin secretion rates return to normal. It can now be said to be established that in the first 10 years after diagnosis, type 2 diabetes can be reversed

to non-diabetic glucose control in the majority of people who achieve 15% or more decrease in body weight by any means.

4. Synthesizing recent information

In 2008, information from study of: liver fat [7, 9]; moderate calorie restriction in type 2 diabetes [8]; and the immediate effect of bariatric surgery [15] led to the Twin Cycle Hypothesis (Figure 1)[6]. This postulated that the accumulation of fat in liver and secondarily in the pancreas would initiate self-reinforcing cycles which would interact to bring about eventual failure of beta cell function and onset of type 2 diabetes. The purpose of formulating the hypothesis was to permit rigorous testing of its predictions.

If the rapid changes in metabolism following bariatric surgery [45] were indeed a consequence of sudden change in calorie balance, then both defects in insulin secretion and hepatic insulin sensitivity should disappear by inducing sudden negative calorie balance. To test the hypothesis a group with type 2 diabetes within 4 years of diagnosis were studied before and during a 600 kcal/day diet [13]. Within 7 days, liver fat decreased by 30% and became similar to that of the matched control group, and hepatic insulin sensitivity normalised. The close association between liver fat content and hepatic glucose production had previously been established [8, 9, 46]. Plasma glucose normalised by day 7 of the diet, but the changes in post-meal blood glucose control were more gradual. Pancreas fat content decreased gradually over 8 weeks to become the same as in the control group, in step with the increase in both first phase and total insulin secretion. Fat content in the islets was not directly measured although it is known that islets take up fat avidly [31] and that islet fat content closely reflects total pancreatic fat content in animal models [47]. In the Counterpoint study, beta cell function was tested by a gold standard method using a stepped glucose infusion with subsequent arginine bolus. The typical very poor glucose-induced initial rapid peak of insulin secretion (the first phase insulin response) was confirmed at baseline in the study. This first phase response increased gradually over 8 weeks of the very low calorie diet to become indistinguishable from that of age and weight matched non-diabetic control subjects. Although a cause and effect relationship between raised intra-

organ fat levels and metabolic effect has not yet been proven, the time course data following dietary intervention study are highly suggestive of a causal link [13].

Further work has defined for how long after diagnosis type 2 diabetes remains reversible [19]. In the Counterbalance study, the mean weight loss of just under 15% represented weight loss of between 8 and 22kg. Whereas 87% of the short-duration group (<4 years) achieved non-diabetic fasting plasma glucose levels immediately after acute weight loss, only 50% of the long-duration group (8-23 years) did so. In a recent audit of bariatric surgery metabolic outcomes, HbA1c of <43mmol/mol (6.1%) was achieved by 62% and 26% respectively in those with duration of diabetes <4 or >8 years respectively [48], reflecting earlier observations [49]. As the duration of diabetes increases, it appears that beta-cells pass a point of no return and become unable to return to fully differentiated endocrine lineages perhaps with apoptosis. Whether this loss of the paracrine effect of the trophic properties of insulin is directly associated with the steadily progressive loss of pancreatic volume and increasing irregularity of the organ remains to be established [33, 50].

Although the Twin Cycle Hypothesis primarily explains the aetiology and underlying pathophysiology of type 2 diabetes, it indicates that reversal of diabetes should be long term if weight remains steady. Previously it has been shown that diabetic individuals post-bariatric surgery remain non-diabetic for up to 10 years unless substantial weight gain occurs [51]. Following dietary weight loss, 6 months of follow up with no weight regain showed that blood glucose control remained normal. Case reports and case series confirm the longer term normal metabolism following dietary weight loss provided weight remains steady [52, 53].

5. Understanding the apparent heterogeneity of type 2 diabetes

It is frequently stated that non-obese people with T2DM have less insulin resistance but a greater beta cell defect than those who are overweight or obese [1, 54-56]. However, insulin resistance increases as a function of increasing BMI, whether or not an individual has normal blood glucose control [57]. When direct comparisons is made between people matched for BMI to determine the impact of insulin resistance on

the development of T2DM, it can be seen that people with T2DM have modestly greater insulin resistance at any level of BMI [58]. When individuals with T2DM are compared with BMI matched late-onset autoimmune diabetes the same is seen [59]. The apparent enigma of the usually higher fasting plasma insulin levels seen in obese individuals with T2DM, compared with their non-diabetic counterparts, is explained when the greater insulin resistance of obesity itself is taken into account [60, 61]. This must not be confused with the fall in fasting plasma insulin levels observed with increasing duration of type 2 diabetes, as this reflects apparently terminal failure of beta cells [19]. Finally, the post-prandial insulin response to test meals is similar in non-obese and obese people with T2DM [62]. Separately, the first phase insulin response to an intravenous glucose challenge is almost absent in T2DM, whatever the BMI, and in impaired glucose tolerance no effect of BMI has been demonstrated on either first or second phase insulin secretion [62].

The concept that non-obese people with T2DM have lesser degrees of insulin resistance and greater beta cell impairment has been extrapolated to therapeutic decisions. The ADA/EASD guidelines make the point that "Common practice has favoured metformin in heavier patients" [63], and non-obese patients are assumed to be able to respond less well to the glucose lowering effect of metformin. This assumption has been examined and disproven: the improvement in HbA_{1c} between matched non-obese and obese groups with T2DM given metformin was almost identical [64, 65].

By assembling this information together with information on the distribution of BMI for the UKPDS, it has been possible to put forward the Personal Fat Threshold concept [66]. This allows understanding that type 2 diabetes only develops if an individual accumulates more fat than can be stored in the metabolically inert subcutaneous depots. The capacity of this depot varies considerably and is probably genetically determined, perhaps modified by early life environment. If however this very individual capacity is exceeded then the fat will accumulate in liver, then pancreas. Whereas 72% of people with BMI over 40kg/m^2 have no diabetes [5], a substantial proportion of people presenting with type 2 diabetes may have a normal BMI (36% in the UKPDS cohort [67]). Dramatically, the Nurses' Health Study shows that developing a BMI between 23-25 is associated with a 4-four increased risk of type 2 diabetes compared with having a BMI of less than 22kg/m2 [68]. In contrast to the population

risk of developing type 2 diabetes, BMI is not necessarily a good guide to management of an individual patient.

The Personal Fat Threshold concept is also reflected in the recent data from the Counterbalance study. It may be thought that fat removed from liver and pancreas by short term hypocaloric dieting might gradually be replaced by the remaining excess from subcutaneous and visceral depots during subsequent isocaloric food intake. If so, follow up would be expected to reveal re-accumulation of intra-pancreatic fat with or without decline in beta-cell function. This has been examined during six months of weight stability after acute weight loss in people with type 2 diabetes [19]. There was no accumulation of fat in either pancreas of liver and first phase insulin response remained normal even though the weight loss of just under 15 kg left half of the group in the obese category, with the rest overweight [19].

6. Understanding the time course of type 2 diabetes

The earliest risk factor for development of type 2 diabetes is believed to be low insulin sensitivity in skeletal muscle. There is no fixed cut off, but those people who will develop diabetes have insulin sensitivity mainly in the lowest population quartile [18]. In pre-diabetic individuals, raised plasma insulin levels compensate and allow normal plasma glucose control. However, as the process of *de novo* lipogenesis is stimulated by higher insulin levels [69] this sets the scene for hepatic fat accumulation as predicted by the Twin Cycle Hypothesis. Excess fat deposition in the liver is present before the onset of classical type 2 diabetes [12, 70-72]. In established type 2 diabetes, liver fat is supra-normal [71]. When ultrasound is used rather than magnetic resonance methods, only more severe degrees of steatosis are detected, and the prevalence of fatty liver is likely to be underestimated. One ultrasound study reported 70% of people with type 2 diabetes as having fatty liver [72]. Nonetheless, even using ultrasound, the prognostic power to predict onset of type 2 diabetes just by presence of hepatic steatosis is impressive. A large study of individuals with normal glucose tolerance at baseline showed a very low 8 year incidence of type 2 diabetes if fatty liver had been excluded at baseline whereas if present the hazard ratio for diabetes was 5.5 (range 3.6-8.5) [70]. The temporal progression from weight gain to raised liver enzymes, onwards to

hypertriglyceridemia and then glucose intolerance is described in the legend to Figure 1 [73]. This has been discussed in a recent review of the aetiology of type 2 diabetes [74].

In obese young people, decreased beta cell function predicts deterioration of glucose tolerance [75, 76]. Also, the rate of decline in glucose tolerance in first-degree relatives of type 2 diabetic individuals is a function of loss of beta-cell competence, whilst insulin sensitivity changes little [77]. In populations with high incidence of type 2 diabetes transition from hyperinsulinaemic normal glucose tolerance to overt diabetes involves a large, rapid rise in glucose levels with a relatively small further loss of acute β-cell competence [78]. Recently, the Whitehall II study has shown in a large population followed prospectively that those people developing diabetes exhibit a sudden rise in fasting glucose as beta cell function deteriorates [79]. This shows the pancreas to respond to an increasing plasma glucose with a normal, brisk insulin response largely in the two years before the detection of diabetes, even though fasting plasma glucose may have been at the upper border of normal for several years. It had previously been assumed that a linear rise in fasting plasma glucose and gradual beta cell decompensation would occur [80].

The Counterbalance study provides some of the clearest information to date on the change to the later, less reversible phase of type 2 diabetes [19]. At baseline, those individuals who could not achieve long term fasting plasma glucose levels of under 7mmol/l by substantial weight loss were characterised not only by low fasting plasma insulin levels but also by strikingly poor first phase insulin responses. Confirming that severe beta cell failure had occurred, the degree of hepatic steatosis had decreased. Taken together, these observations suggest that eventually, and most commonly after 10 years of type 2 diabetes, the beta cells pass beyond a state of reversible de-differentiation to a relatively irreversible loss of ability to make insulin.

It has been accepted for some time that the beta cell dysfunction of established diabetes progresses in an inevitable manner from the time of diagnosis [3, 77, 81] even though insulin resistance can be modified at least to some extent. However, it is now clear that the beta cell defect, and not solely hepatic insulin resistance, may be entirely reversed by weight loss at least early in the course of type 2 diabetes [13, 82]. The low insulin sensitivity of muscle tissue does not change materially either during the onset of

diabetes or during any subsequent reversal. Overall, the recent information on the inhibitory effects of excess fat on beta cell function and gene expression permits a new understanding of the time course of type 2 diabetes, both during the pre-diabetic phase and in the years after diagnosis.

7. Expert Commentary and Five Year View

Once the methodology to achieve precise quantitation of intra-pancreatic fat is more widely applied, studies in different ethnic groups can be launched. This will allow an approach to the genetic determinants of intra-pancreatic fat accumulation. The process of supplying fatty acids to the pancreas will require detailed study. Dietary calorie restraint allows correction of all the metabolic features of type 2 diabetes, and it can be considered that pharmacological means could mimic some aspects of this metabolic normalisation.

8. Key Issues

- The predictions of the Twin Cycle Hypothesis have been borne out by recent in vivo studies on reversing type 2 diabetes
- In the first 10 years of type 2 diabetes for most people: Negative calorie balance rapidly normalises liver fat content, hepatic glucose production and fasting plasma glucose; and if the negative calorie balance is sustained, intra-pancreatic fat content and insulin secretion also normalize
- After around 10 years of type 2 diabetes, beta cells enter a phase of failure which is not reversible by decrease in fat supply
- For any one individual, type 2 diabetes develops some years after a Personal fat Threshold has been exceeded. If the total fat load of the body is decreased below this constitutionally determined threshold then the condition may be entirely reversible

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Declaration of interest

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** of considerable interest

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Reference Annotations

[7] This study demonstrated clearly the link between liver fat content and insulin sensitivity of the liver.

[8] This work demonstrates that the fatty liver of type 2 diabetes would respond to moderate calorie restriction with improvement in fasting plasma glucose.

[11] Overfeeding carbohydrate produces a rapid increase in liver fat content.

[6] This summarized the information which allowed postulation of the Twin Cycle Hypothesis

[13] The Counterpoint study tested the basic predictions of the Twin Cycle Hypothesis and confirmed the underlying postulates.

[33] This paper reports the abnormal gross morphology of the pancreas in type 2 diabetes and shows why measurement of pancreatic fat content is so technically demanding.

[19] The Counterbalance study showed that type 2 diabetes becomes less likely to be reversed by substantial weight loss after around 10 years after diagnosis, and also that the return to non-diabetic glucose control is durable on an isocaloric diet.

[83] This study shows that equivalent weight loss in people with normal glucose tolerance or with type 2 diabetes produces decrease in pancreatic fat content only in type 2 diabetes.

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Legend to Figure

The Twin Cycle Hypothesis. During chronic, excess calorie intake, particularly in the presence of muscle insulin resistance, the raised plasma insulin levels will expedite chronic excess calorie storage from carbohydrate via *de novo* lipogenesis. This tends to promote storage of fat in the liver very gradually over years. This will cause the liver to become increasingly resistant to insulin and a small increase in plasma glucose will tend to occur. In turn insulin secretion will increase to control plasma glucose down. The further increased insulin levels will bring about a self-reinforcing vicious cycle. Excess liver fat will inevitably lead to an increased rate of export of VLDL triglyceride from the liver. Amongst other tissue, islets will be exposed to higher rates of fatty acid supply and pancreas fat levels as a whole will increase. The increased exposure to fatty acid metabolites will bring about endoreticulum stress, and eventually beta cell de-differentiation, with relative inhibition of meal insulin secretion. The vicious cycles will interact over at least 10 years. At a personal threshold, the pancreas fat becomes too great a load, and plasma glucose levels will then rise relatively rapidly. The Figure is redrawn from reference [6] and previously published in this form [74].