Type 2 Diabetes

Etiology and reversibility

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Reversal of type 2 diabetes to normal metabolic control by either bariatric surgery or hypocaloric diet allows for the time sequence of underlying pathophysiologic mechanisms to be observed. In reverse order, the same mechanisms are likely to determine the events leading to the onset of hyperglycemia and permit insight into the etiology of type 2 diabetes. Within 7 days of instituting a substantial negative calorie balance by either dietary intervention or bariatric surgery, fasting plasma glucose levels can normalize. This rapid change relates to a substantial fall in liver fat content and return of normal hepatic insulin sensitivity. Over 8 weeks, first phase and maximal rates of insulin secretion steadily return to normal, and this change is in step with steadily decreasing pancreatic fat content. The difference in time course of these two processes is striking. Recent information on the intracellular effects of excess lipid intermediaries explains the likely biochemical basis, which simplifies both the basic understanding of the condition and the concepts used to determine appropriate management. Recent large, long-duration population studies on time course of plasma glucose and insulin secretion before the diagnosis of diabetes are consistent with this new understanding. Type 2 diabetes has long been regarded as inevitably progressive, requiring increasing numbers of oral hypoglycemic agents and eventually insulin, but it is now certain that the disease process can be halted with restoration of normal carbohydrate and fat metabolism. Type 2 diabetes can be understood as a potentially reversible metabolic state precipitated by the single cause of chronic excess intraorgan fat.

Type 2 diabetes has long been known to progress despite glucose-lowering treatment, with 50% of individuals requiring insulin therapy within 10 years (1). This seemingly inexorable deterioration in control has been interpreted to mean that the condition is treatable but not curable. Clinical guidelines recognize this deterioration with algorithms of sequential addition of therapies. Insulin resistance and β-cell dysfunction are known to be the major pathophysiologic factors driving type 2 diabetes; however, these factors come into play with very different time courses. Insulin resistance in muscle is the earliest detectable abnormality of type 2 diabetes (2). In contrast, changes in insulin secretion determine both the onset of hyperglycemia and the progression toward insulin therapy (3,4). The etiology of each of these two major factors appears to be distinct. Insulin resistance may be caused by an insulin signaling defect (5), glucose transporter defect (6), or lipotoxicity (7), and β-cell dysfunction is postulated to be caused by amyloid deposition in the islets (8), oxidative stress (9), excess fatty acid (10), or lack of incretin effect (11). The demonstration of reversibility of type 2 diabetes offers the opportunity to evaluate the time sequence of pathophysiologic events during return to normal glucose metabolism and, hence, to unraveling the etiology.

Reversal of type 2 diabetes by bariatric surgery

The first hint that type 2 diabetes is a fully reversible syndrome came from bariatric surgery. Almost a quarter century ago, Pories et al. (12) demonstrated that blood glucose levels normalized in obese people with type 2 diabetes undergoing bariatric surgery and that 10 years later, almost 90% remained free of diabetes. The phenomenon was more recently tested in a randomized prospective study comparing gastric banding with intensive medical therapy for type 2 diabetes (13). This least invasive type of surgery was most suitable for the randomized study, although it was associated with lower rates of diabetes reversal than other procedures. Mean fasting plasma glucose fell to normal levels in the surgically treated group but declined only modestly in the intensive medical treatment group despite oral agents and insulin (Fig. 1) (13). Remission of diabetes was related to the degree of weight loss rather than to group allocation and was achieved in 73% of the surgical group and 13% of the intensive medical treatment group because surgery was more effective in achieving weight loss as previously
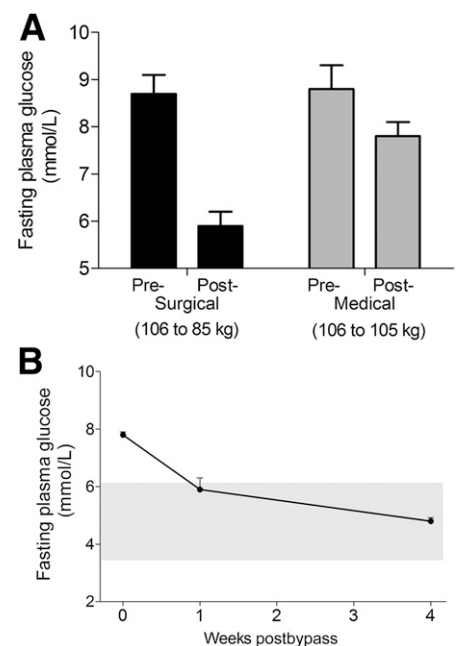

Figure 1—A: *Fasting plasma glucose and weight change 2 years after randomization either to gastric banding or to intensive medical therapy for weight loss and glucose control. Data plotted with permission from Dixon et al. (13). B: Early changes in fasting plasma glucose level following pancreatoduodenal bypass surgery. A decrease into the normal range was seen within 7 days. Reproduced with permission from Taylor (98).*

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described (14). Type 2 diabetes can be reversed by applying a surgical procedure that diminishes fat mass.

However, the observation that normalization of glucose in type 2 diabetes occurred within days after bariatric surgery, before substantial weight loss (15), led to the widespread belief that surgery itself brought about specific changes mediated through incretin hormone secretion (16,17). This reasoning overlooked the major change that follows bariatric surgery: an acute, profound decrease in calorie intake. Typically, those undergoing bariatric surgery have a mean body weight of ~150 kg (15) and would therefore require a daily calorie intake of ~13.4 MJ/day (3,200 kcal/day) for weight maintenance (18). This intake decreases precipitously at the time of surgery. The sudden reversal of traffic into fat stores brings about a profound change in intracellular concentration of fat metabolites. It is known that under hypocaloric conditions, fat is mobilized first from the liver and other ectopic sites rather than from visceral or subcutaneous fat stores (19). This process has been studied in detail during more moderate calorie restriction in type 2 diabetes over 8 weeks (20). Fasting plasma glucose was shown to be improved because of an 81% decrease in liver fat content and normalization of hepatic insulin sensitivity with no change in the insulin resistance of muscle.

Reversal of type 2 diabetes by diet alone

—If the rapid changes in metabolism following bariatric surgery are a consequence of the sudden change in calorie balance, the defects in both insulin secretion and hepatic insulin sensitivity of type 2 diabetes should be correctable by change in diet alone. To test this hypothesis, a group of people with type 2 diabetes were studied before and during a 600 kcal/day diet (21). Within 7 days, liver fat decreased by 30%, becoming similar to that of the control group, and hepatic insulin sensitivity normalized (Fig. 2). The close association between liver fat content and hepatic glucose production had previously been established (20,22,23). Plasma glucose normalized by day 7 of the diet.

During this 8-week study, β-cell function was tested by a gold standard method that used a stepped glucose infusion with subsequent arginine bolus (21). In type 2 diabetes, the glucose-induced initial rapid peak of insulin secretion
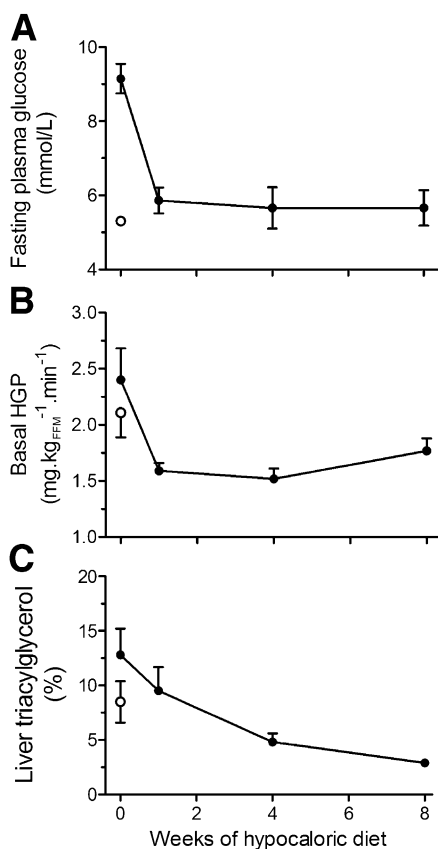
Figure 2—*Effect of a very-low-calorie diet in type 2 diabetes on fasting plasma glucose level (A), basal hepatic glucose production (HGP) (B), and hepatic triacylglycerol content (C). For comparison, data for a matched nondiabetic control group are shown as ◯. Reproduced with permission from Lim et al. (21). FFM, fat-free mass.*

(the first phase insulin response) typically is absent. This was confirmed at baseline in the study, but the first phase response increased gradually over 8 weeks of a very-low-calorie diet to become indistinguishable from that of age- and weight-matched nondiabetic control subjects. The maximum insulin response, as elicited by arginine bolus during hyperglycemia, also normalized. Pancreas fat content decreased gradually during the study period to become the same as that in the control group, a time course matching that of the increase in both first phase and total insulin secretion (Fig. 3). Fat content in the islets was not directly measured, although it is known that islets take up fat avidly (24) and that islet fat content closely reflects total pancreatic fat content in animal models (25). Although a cause-and-effect relationship between raised intraorgan fat levels and metabolic effect has not yet been proven, the time course

data following the dietary intervention study are highly suggestive of a causal link (21).

New perspectives on insulin resistance

Muscle
Whole-body insulin resistance is the earliest predictor of type 2 diabetes onset, and this mainly reflects muscle insulin resistance (26). However, careful separation of the contributions of muscle and liver have shown that early improvement in control of fasting plasma glucose level is associated only with improvement in liver insulin sensitivity (20,21). It is clear that the resumption of normal or near-normal diurnal blood glucose control does not require improvement in muscle insulin sensitivity. Although this finding 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 (27). Humans who have the *PPP1R3A* genetic variant of muscle glycogen synthase cannot store glycogen in muscle after meals but are not necessarily hyperglycemic (28). Many normoglycemic individuals maintain normal blood glucose levels with a degree of muscle insulin resistance identical to those with type 2 diabetes (29).

Although a defect in mitochondrial function is associated with extremes of insulin resistance in skeletal muscle (30), this does not appear to be relevant to the etiology of type 2 diabetes. No defect is present in early type 2 diabetes but rather is directly related to ambient plasma glucose concentration (31). Observed rates of mitochondrial ATP production can be modified by increasing or decreasing plasma fatty acid concentration (32,33). Additionally, the onset of insulin stimulation of mitochondrial ATP synthesis is slow, gradually increasing over 2 h, and quite distinct from the acute onset of insulin's metabolic effects (34). Although it remains possible that secondary mitochondrial effects of hyperglycemia and excess fatty acids exist, there is no evidence for a primary mitochondrial defect underlying type 2 diabetes.

The physiologic importance of muscle insulin resistance is likely to operate over a period of many years. The presence of long-standing muscle insulin resistance will not of itself cause blood glucose levels to rise, but raised plasma insulin levels will expedite accumulation
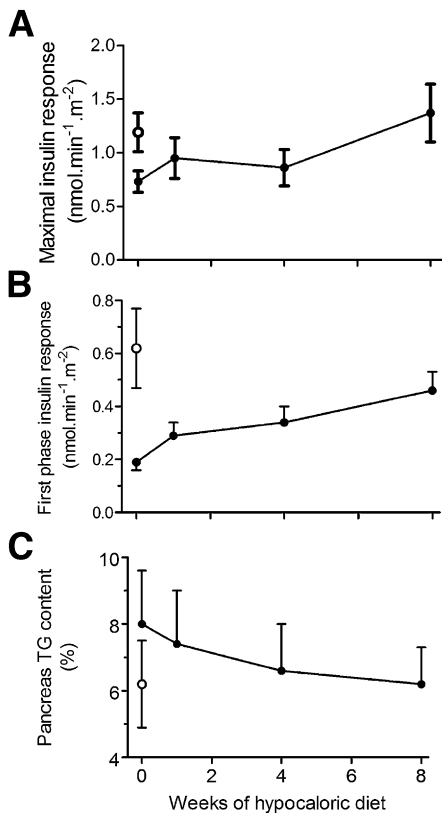
Figure 3—*Effect of an 8-week very-low-calorie diet in type 2 diabetes on arginine-induced maximal insulin secretion (A), first phase insulin response to a 2.8 mmol/L increase in plasma glucose (B), and pancreas triacylglycerol (TG) content (C). For comparison, data for a matched nondiabetic control group are shown as ○. Replotted with permission from Lim et al. (21).*

of liver fat by stimulation of de novo lipogenesis (26).

Liver

Evidence linking hepatic insulin sensitivity to intraorgan triglyceride content has been steadily accumulating. In insulin-treated type 2 diabetes, insulin dose correlates with the extent of fatty liver (35), and in turn, this is associated with insulin sensitivity to suppression of hepatic glucose production (36). Decreasing the fat content of liver is associated with improvement in insulin suppression of glucose production and, thereby, with improvement in fasting plasma glucose (20,23).

Storage of liver fat can only occur when daily calorie intake exceeds expenditure. Sucrose overfeeding for 3 weeks has been shown to cause a 30% increase in liver fat content (37). The associated metabolic stress on hepatocytes was reflected by a simultaneous 30% rise in serum alanine aminotransferase (ALT)

levels, and both liver fat and serum ALT returned to normal levels during a subsequent hypocaloric diet. Superimposed upon a positive calorie balance, the extent of portal vein hyperinsulinemia determines how rapidly conversion of excess sugars to fatty acid occurs in the liver. In groups of both obese and nonobese subjects, it was found that those with higher plasma insulin levels have markedly increased rates of hepatic de novo lipogenesis (2,38,39). Conversely, in type 1 diabetes the relatively low insulin concentration in the portal vein (as a consequence of insulin injection into subcutaneous tissue) is associated with subnormal liver fat content (40). Initiation of subcutaneous insulin therapy in type 2 diabetes brings about a decrease in portal insulin delivery by suppression of pancreatic insulin secretion and, hence, a decrease in liver fat (41). Hypocaloric diet (42), physical activity (43), or thiazolidinedione use (23,44) each reduces insulin secretion and decreases liver fat content. Newly synthesized triacylglycerol in the liver will be either oxidized, exported, or stored as hepatic triacylglycerol. Because transport of fatty acid into mitochondria for oxidation is inhibited by the malonyl-CoA produced during de novo lipogenesis, newly synthesized triacylglycerol is preferentially directed toward storage or export. Hence, hepatic fat content and plasma VLDL triacylglycerol levels are increased.

Within the hepatocyte, fatty acids can only be derived from de novo lipogenesis, uptake of nonesterified fatty acid and LDL, or lipolysis of intracellular triacylglycerol. The fatty acid pool may be oxidized for energy or may be combined with glycerol to form mono-, di-, and then triacylglycerols. It is possible that a lower ability to oxidize fat within the hepatocyte could be one of several susceptibility factors for the accumulation of liver fat (45). Excess diacylglycerol has a profound effect on activating protein kinase C epsilon type (PKCε), which inhibits the signaling pathway from the insulin receptor to insulin receptor substrate 1 (IRS-1), the first postreceptor step in intracellular insulin action (46). Thus, under circumstances of chronic energy excess, a raised level of intracellular diacylglycerol specifically prevents normal insulin action, and hepatic glucose production fails to be controlled (Fig. 4). High-fat feeding of rodents brings about raised levels of diacylglycerol, PKCε activation, and insulin resistance. However, if fatty acids are preferentially oxidized rather than
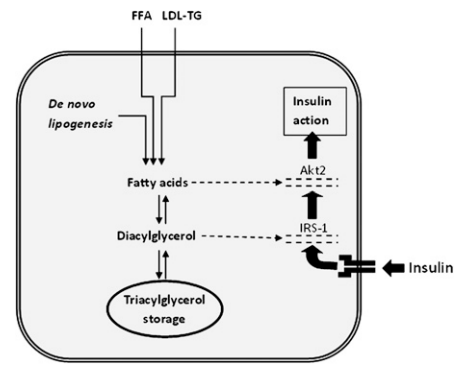

Figure 4—*Mechanism of interaction between excess amounts of fatty acids, diacylglycerol, and ceramide and insulin action within the hepatocyte. Diacylglycerol activates PKCε and inhibits activation of IRS-1 by the insulin receptor. Ceramides cause sequestration of Akt2 by PKCζ and inhibit insulin control of gluconeogenesis. These mechanisms have recently been reviewed (99). FFA, free-fatty acid; TG, triacylglycerol.*

esterified to diacylglycerol, then PKCε activation is prevented, and hepatic insulin sensitivity is maintained. The molecular specificity of this mechanism has been confirmed by use of antisense oligonucleotide to PKCε, which prevents hepatic insulin resistance despite raised diacylglycerol levels during high-fat feeding (47). In obese humans, intrahepatic diacylglycerol concentration has been shown to correlate with hepatic insulin sensitivity (48,49). Additionally, the presence of excess fatty acids promotes ceramide synthesis by esterification with sphingosine. Ceramides cause sequestration of Akt2 and activation of gluconeogenic enzymes (Fig. 4), although no relationship with in vivo insulin resistance could be demonstrated in humans (49). However, the described intracellular regulatory roles of diacylglycerol and ceramide are consistent with the in vivo observations of hepatic steatosis and control of hepatic glucose production (20,21).

Fasting plasma glucose concentration depends entirely on the fasting rate of hepatic glucose production and, hence, on its sensitivity to suppression by insulin. Hepatic insulin sensitivity cannot be inferred from observed postprandial change in hepatic glycogen concentration because glucose transport into the hepatocyte is not rate limiting, unlike in muscle, and hyperglycemia itself drives the process of glycogen synthesis irrespective of insulin action. Indeed, postprandial glycogen storage in liver has been shown to be moderately impaired in type 2 diabetes

(50) compared with the marked impairment in skeletal muscle (51).

Although a close relationship exists among raised liver fat levels, insulin resistance, and raised liver enzyme levels (52), high levels of liver fat are not inevitably associated with hepatic insulin resistance. This is analogous to the discordance observed in the muscle of trained athletes in whom raised intramyocellular triacylglycerol is associated with high insulin sensitivity (53). This relationship is also seen in muscle of mice overexpressing the enzyme DGAT-1, which rapidly esterifies diacylglycerol to metabolically inert triacylglycerol (54). In both circumstances, raised intracellular triacylglycerol stores coexist with normal insulin sensitivity. When a variant of *PNPLA3* was described as determining increased hepatic fat levels, it appeared that a major factor underlying nonalcoholic fatty liver disease and insulin resistance was identified (55). However, this relatively rare genetic variant is not associated with hepatic insulin resistance (56). Because the responsible G allele of *PNPLA3* is believed to code for a lipase that is ineffective in triacylglycerol hydrolysis, it appears that diacylglycerol and fatty acids are sequestered as inert triacylglycerol, preventing any inhibitory effect on insulin signaling.

New perspectives on the β-cell defect
—Chronic exposure of β-cells to triacylglycerol or fatty acids either in vitro or in vivo decreases β-cell capacity to respond to an acute increase in glucose levels (57,58). This concept is far from new (59,60), but the observations of what happens during reversal of diabetes provide a new perspective. β-Cells avidly import fatty acids through the CD36 transporter (24,61) and respond to increased fatty acid supply by storing the excess as triacylglycerol (62). The cellular process of insulin secretion in response to an increase in glucose supply depends on ATP generation by glucose oxidation. However, in the context of an oversupply of fatty acids, such chronic nutrient surfeit prevents further increases in ATP production. Increased fatty acid availability inhibits both pyruvate cycling, which is normally increased during an acute increase in glucose availability, and pyruvate dehydrogenase activity, the major rate-limiting enzyme of glucose oxidation (63). Fatty acids have been shown to inhibit β-cell proliferation in vitro by induction of the cell cycle inhibitors p16

and p18, and this effect is magnified by increased glucose concentration (64). This antiproliferative effect is specifically prevented by small interfering RNA knockdown of the inhibitors. In the Zucker diabetic fatty rat, a genetic model of spontaneous type 2 diabetes, the onset of hyperglycemia is preceded by a rapid increase in pancreatic fat (58). It is particularly noteworthy that the onset of diabetes in this genetic model is completely preventable by restriction of food intake (65), illustrating the interaction between genetic susceptibility and environmental factors.

Clearly separate from the characteristic lack of acute insulin secretion in response to increase in glucose supply is the matter of total mass of β-cells. The former determines the immediate metabolic response to eating, whereas the latter places a long-term limitation on total possible insulin response. Histological studies of the pancreas in type 2 diabetes consistently show an ~50% reduction in number of β-cells compared with normal subjects (66). β-Cell loss appears to increase as duration of diabetes increases (67). The process is likely to be regulated by apoptosis, a mechanism known to be increased by chronic exposure to increased fatty acid metabolites (68). Ceramides, which are synthesized directly from fatty acids, are likely mediators of the lipid effects on apoptosis (10,69). In light of new knowledge about β-cell apoptosis and rates of turnover during adult life, it is conceivable that removal of adverse factors could result in restoration of normal β-cell number, even late in the disease (66,70). Plasticity of lineage and transdifferentiation of human adult β-cells could also be relevant, and the evidence for this has recently been reviewed (71). β-Cell number following reversal of type 2 diabetes remains to be examined, but overall, it is clear that at least a critical mass of β-cells is not permanently damaged but merely metabolically inhibited.

A wide scatter of absolute levels of pancreas triacylglycerol has been reported, with a tendency for higher levels in people with diabetes (57). This large population study showed overlap between diabetic and weight-matched control groups. These findings were also observed in a more recent smaller study that used a more precise method (21). Why would one person have normal β-cell function with a pancreas fat level of, for example, 8%, whereas another has type 2 diabetes with a pancreas fat

level of 5%? There must be varying degrees of liposusceptibility of the metabolic organs, and this has been demonstrated in relation to ethnic differences (72). If the fat is simply not available to the body, then the susceptibility of the pancreas will not be tested, whereas if the individual acquires excess fat stores, then β-cell failure may or may not develop depending on degree of liposusceptibility. In any group of people with type 2 diabetes, simple inspection reveals that diabetes develops in some with a body mass index (BMI) in the normal or overweight range, whereas others have a very high BMI. The pathophysiologic changes in insulin secretion and insulin sensitivity are not different in obese and normal weight people (73), and the upswing in population rates of type 2 diabetes relates to a right shift in the whole BMI distribution. Hence, the person with a BMI of 24 and type 2 diabetes would in a previous era have had a BMI of 21 and no diabetes. It is clear that individual susceptibility factors determine the onset of the condition, and both genetic and epigenetic factors may contribute. Given that diabetes cannot occur without loss of acute insulin response to food, it can be postulated that this failure of acute insulin secretion could relate to both accumulation of fat and susceptibility to the adverse effect of excess fat in the pancreas.

The time course to development of type 2 diabetes
—The earliest predictor of the development of type 2 diabetes is low insulin sensitivity in skeletal muscle, but it is important to recognize that this is not a distinct abnormality but rather part of the wide range expressed in the population. Those people in whom diabetes will develop simply have insulin sensitivity, mainly in the lowest population quartile (29). In prediabetic individuals, raised plasma insulin levels compensate and allow normal plasma glucose control. However, because the process of de novo lipogenesis is stimulated by higher insulin levels (38), the scene is set for hepatic fat accumulation. Excess fat deposition in the liver is present before the onset of classical type 2 diabetes (43,74–76), and in established type 2 diabetes, liver fat is supranormal (20). When ultrasound rather than magnetic resonance imaging is used, only more-severe degrees of steatosis are detected, and the prevalence of fatty liver is underestimated, with estimates of 70% of people with type 2

diabetes as having a fatty liver (76). Nonetheless, the prognostic power of merely the presence of a fatty liver is impressive of predicting the onset of type 2 diabetes. 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) (74). In support of this finding, a temporal progression from weight gain to raised liver enzyme levels and onward to hypertriglyceridemia and then glucose intolerance has been demonstrated (77).

In obese young people, decreased β-cell function has recently been shown to predict deterioration of glucose tolerance (4,78). Additionally, the rate of decline in glucose tolerance in first-degree relatives of type 2 diabetic individuals is strongly related to the loss of β-cell function, whereas insulin sensitivity changes little (79). This observation mirrors those in populations with a high incidence of type 2 diabetes in which transition from hyperinsulinemic normal glucose tolerance to overt diabetes involves a large, rapid rise in glucose levels as a result of a relatively small further loss of acute β-cell competence (3). The Whitehall II study showed in a large population followed prospectively that people with diabetes exhibit a sudden rise in fasting glucose as β-cell function deteriorates (Fig. 5) (80). Hence, the ability of the pancreas to mount a normal, brisk insulin response to an increasing plasma glucose level is lost in the 2 years before the detection of diabetes, although fasting plasma glucose levels may have been at the upper limit of normal for several years. This was very different from the widely assumed linear rise in fasting plasma glucose level and gradual β-cell decompensation but is consistent with the time course of markers of increased liver fat before the onset of type 2 diabetes observed in other studies (81). Data from the West of Scotland Coronary Prevention Study demonstrated that plasma triacylglycerol and ALT levels were modestly elevated 2 years before the diagnosis of type 2 diabetes and that there was a steady rise in the level of this liver enzyme in the run-up to the time of diagnosis (75).

The accepted view has been that the β-cell dysfunction of established diabetes progresses inexorably (79,82,83), whereas insulin resistance can be modified at least to some extent. However, it is now
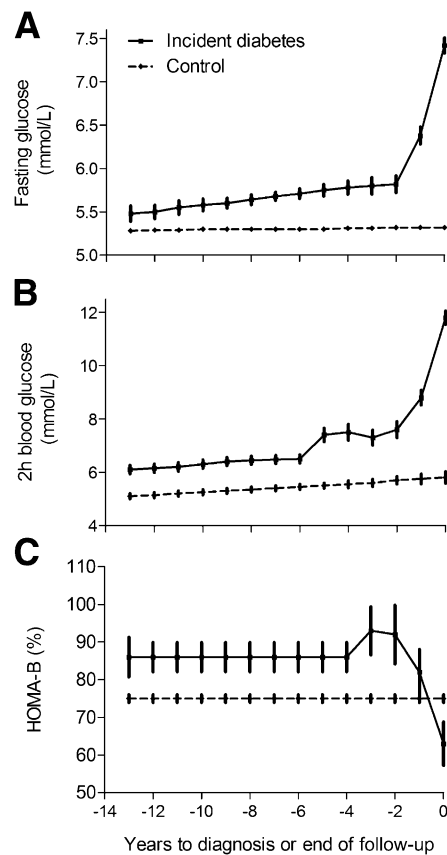

Figure 5—*Change in fasting plasma glucose (A), 2 h post-oral glucose tolerance test (B), and homeostasis model assessment (HOMA-B) insulin secretion (C) during the 16-year follow-up in the Whitehall II study. Of the 6,538 people studied, diabetes developed in 505. Time 0 was taken as the diagnosis of diabetes or as the end of follow-up for those remaining normoglycemic. Redrawn with permission from Tabák et al. (80).*

clear that the β-cell defect, not solely hepatic insulin resistance, may be reversible by weight loss at least early in the course of type 2 diabetes (21,84). The low insulin sensitivity of muscle tissue does not change materially either during the onset of diabetes or during subsequent reversal. Overall, the information on the inhibitory effects of excess fat on β-cell function and apoptosis permits a new understanding of the etiology and time course of type 2 diabetes.

The twin cycle hypothesis of etiology of type 2 diabetes—Together with evidence of normalization of insulin secretion after bariatric surgery (84), insights into the behavior of the liver and pancreas during hypocaloric dieting lead to a hypothesis of the etiology and pathogenesis of type 2

diabetes (Fig. 6): The accumulation of fat in liver and secondarily in the pancreas will lead to self-reinforcing cycles that interact to bring about type 2 diabetes. Fatty liver leads to impaired fasting glucose metabolism and increases export of VLDL triacylglycerol (85), which increases fat delivery to all tissues, including the islets. The liver and pancreas cycles drive onward after diagnosis with steadily decreasing β-cell function. However, of note, observations of the reversal of type 2 diabetes confirm that if the primary influence of positive calorie balance is removed, then the processes are reversible (21).

How long will diabetes stay away after weight loss? Long-term normal blood glucose control in previously diabetic individuals after bariatric surgery demonstrates that diabetes does not recur for up to 10 years, unless substantial weight gain occurs (86). These observations are consistent with the twin cycle hypothesis and the existence of a trigger level for adverse metabolic effects of fat in the pancreas. Hence, for a given individual with type 2 diabetes, reducing the liver and pancreas fat content below his or her personal trigger levels would be expected to result in a release from the fatty acid–mediated dysfunction. Individual tolerance of different degrees of fat exposure vary, and understanding this liposusceptibility will underpin the future understanding of genetically determined risk in any given environment. However, this should not obscure the central point: If a person has type 2 diabetes, there is more fat in the liver and pancreas than he or she can cope with.

Implication for management of type 2 diabetes—The extent of weight loss required to reverse type 2 diabetes is much greater than conventionally advised. A clear distinction must be made between weight loss that improves glucose control but leaves blood glucose levels abnormal and weight loss of sufficient degree to normalize pancreatic function. The Belfast diet study provides an example of moderate weight loss leading to reasonably controlled, yet persistent diabetes. This study showed that a mean weight loss of 11 kg decreased fasting blood glucose levels from 10.4 to 7.0 mmol/L but that this abnormal level presaged the all-too-familiar deterioration of control (87).

Data from the Swedish randomized study of gastric banding showed that a loss of 20% body weight was associated
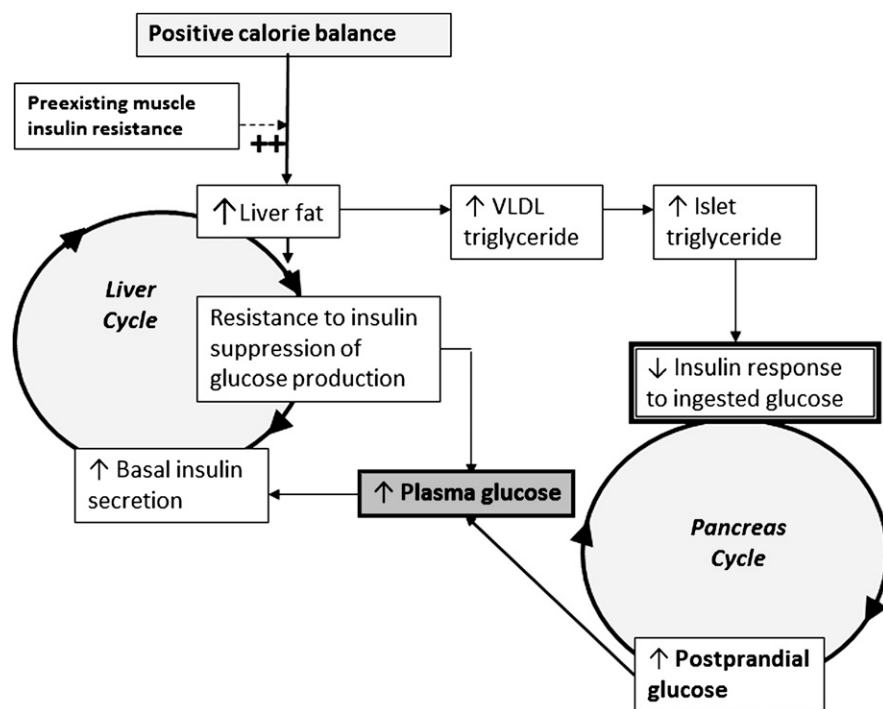
Figure 6—*The twin cycle hypothesis of the etiology of type 2 diabetes. During long-term intake of more calories than are expended each day, any excess carbohydrate must undergo de novo lipogenesis, which particularly promotes fat accumulation in the liver. Because insulin stimulates de novo lipogenesis, individuals with a degree of insulin resistance (determined by family or lifestyle factors) will accumulate liver fat more readily than others because of higher plasma insulin levels. In turn, the increased liver fat will cause relative resistance to insulin suppression of hepatic glucose production. Over many years, a modest increase in fasting plasma glucose level will stimulate increased basal insulin secretion rates to maintain euglycemia. The consequent hyperinsulinemia will further increase the conversion of excess calories to liver fat. A cycle of hyperinsulinemia and blunted suppression of hepatic glucose production becomes established. Fatty liver leads to increased export of VLDL triacylglycerol (85), which will increase fat delivery to all tissues, including the islets. This process is further stimulated by elevated plasma glucose levels (85). Excess fatty acid availability in the pancreatic islet would be expected to impair the acute insulin secretion in response to ingested food, and at a certain level of fatty acid exposure, postprandial hyperglycemia will supervene. The hyperglycemia will further increase insulin secretion rates, with consequent enhancement of hepatic lipogenesis, spinning the liver cycle faster and driving the pancreas cycle. Eventually, the fatty acid and glucose inhibitory effects on the islets reach a trigger level that leads to a relatively sudden onset of clinical diabetes. Figure adapted with permission from Taylor (98).*

with long-term remission in 73% of a bariatric surgery group, with weight change itself being the principal determinant of glucose control (13). Dietary weight loss of 15 kg allowed for reversal of diabetes in a small group of individuals recently receiving a diagnosis (21). In individuals strongly motivated to regain normal health, substantial weight loss is entirely possible by decreasing food consumption (88). This information should be made available to all people with type 2 diabetes, even though with present methods of changing eating habits, it is unlikely that weight loss can be achieved in those not strongly motivated to escape from diabetes. Some genetic predictors,

especially the Ala12 allele at *PPARG*, of successful long-term weight loss have been identified (89), and use of such markers could guide future therapy. It must be noted that involuntary food shortage, such as a result of war, results in a sharp fall in type 2 diabetes prevalence (90,91).

The role of physical activity must be considered. Increased levels of daily activity bring about decreases in liver fat stores (43), and a single bout of exercise substantially decreases both de novo lipogenesis (39) and plasma VLDL (92). Several studies demonstrated that calorie control combined with exercise is much more successful than calorie restriction

alone (93). However, exercise programs alone produce no weight loss for overweight middle-aged people (94). The necessary initial major loss of body weight demands a substantial reduction in energy intake. After weight loss, steady weight is most effectively achieved by a combination of dietary restriction and physical activity. Both aerobic and resistance exercise are effective (95). The critical factor is sustainability.

Formal recommendations on how to reverse type 2 diabetes in clinical practice must await further studies. In the meantime, it will be helpful for all individuals with newly diagnosed type 2 diabetes to know that they have a metabolic syndrome that is reversible. They should know that if it is not reversed, the consequences for future health and cost of life insurance are dire, although these serious adverse effects must be balanced against the difficulties and privations associated with a substantial and sustained change in eating patterns. For many people, this may prove to be too high a price to pay, but for those who are strongly motivated to escape from type 2 diabetes, the new understanding gives clear direction. Physicians need to accept that long-term weight loss is achievable for a worthwhile proportion of patients (96). In the United States, diabetes costs $174 billion annually (97), and in the United Kingdom, it accounts for 10% of National Health Service expenditure. Even if only a small proportion of patients with type 2 diabetes return to normal glucose control, the savings in disease burden and economic cost will be enormous.

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