

Targeting beta-cell preservation in the management of type 2 diabetes

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Abstract

Type 2 diabetes (T2D) is widely considered a chronic and progressive disease without cure. As beta-cell function progressively declines over time, blood glucose rises. Current management of T2D involves incremental introduction of dietary and drug therapies to achieve normoglycaemia. However, recent studies have demonstrated remission of T2D following bariatric surgery, very low calorie diet or intensive insulin therapy, raising the possibility that the declining beta-cell function in T2D may be arrested or even reversed. The point at which such interventions are introduced in the course of T2D is key for clinical benefit. Future treatment strategies should be revised to target early beta-cell preservation and thus disease remission. This article reviews the pathogenesis of beta-cell dysfunction and evidence for the clinical benefit of preserving beta-cell function in T2D, and discusses the evidence for beta-cell preservation of current glucose-lowering therapies with particular reference to their effect when initiated at the time of diagnosis of T2D.

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Introduction

Type 2 diabetes (T2D) is widely considered a chronic progressive disease with no disease-modifying treatment or cure. Over time, blood glucose rises despite treatment escalation, as beta-cell function progressively declines.¹ However, more recently, studies demonstrating restoration of normoglycaemia following bariatric surgery, very low-calorie diet (VLCD) or intensive insulin therapy (IIT) have raised the possibility that declining beta-cell function in T2D may be arrested or reversed.²⁻⁴

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This article reviews the pathogenesis of beta-cell dysfunction and evidence for the clinical benefit of preserving beta-cell function in T2D. We then discuss the evidence for beta-cell preservation of current glucose-lowering therapies, with particular reference to their effect when initiated at the time of diagnosis of T2D.

Current diabetes management and challenges

The goals of T2D management are to ameliorate the symptoms of hyperglycaemia and reduce the incidence of micro- and macrovascular complications. Current practice is to introduce glucose-lowering therapy in a stepwise fashion: lifestyle intervention followed by oral agents or glucagon-like peptide-1 (GLP-1) as monotherapy (then in combination), and finally insulin therapy.⁵ However, 34% of individuals with T2D do not achieve glycaemic targets.⁶ Five years after diagnosis, only 5% of patients remain free from glucose-lowering medication and 50% of individuals require insulin therapy.⁷

The beta-cell in the pathophysiology of T2D

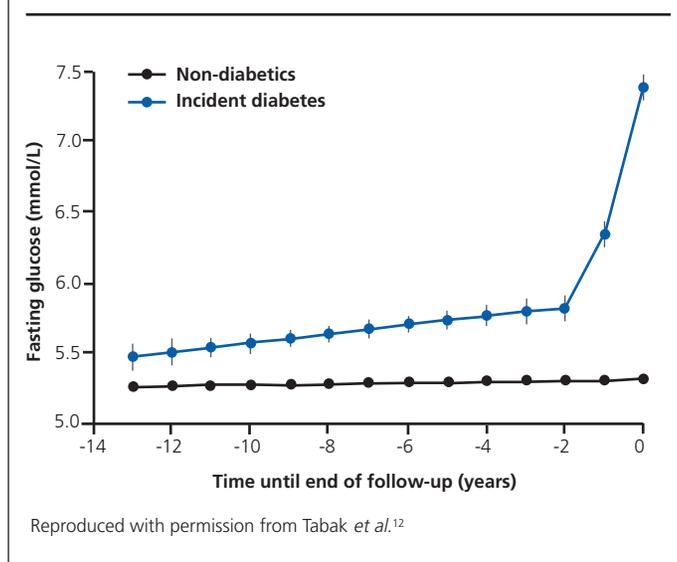
Development of T2D requires both insulin resistance in muscle and liver and impaired beta-cell insulin secretion, although the contribution of each can vary. An increased rate of adipocyte lipolysis, diminished gastrointestinal tract incretin release, hyperglucagonaemia, reduced renal glucose excretion and brain insulin sensitivity also play important roles in glucose intolerance.⁸ Individuals with normal glucose tolerance can have wide variation in insulin sensitivity, yet glucose tolerance remains normal through beta-cell hypersecretion.⁹ Transition from impaired glucose tolerance (IGT) to T2D occurs once beta-cells fail to compensate for insulin resistance.¹⁰

The proposed sequence of pathological events starts with energy excess causing increased hepatic fat, a process which is accelerated by peripheral insulin resistance causing hyperinsulinaemia. Increased hepatic fat causes hepatic insulin resistance with failure to suppress fasting glucose production. Exposure of the beta-cells to excess fatty acids derived from circulating and locally deposited triacylglycerol suppresses glucose-mediated insulin secretion.¹¹

This decline in beta-cell function starts several years before the diagnosis of T2D; the Whitehall II study demonstrated gradually increasing fasting plasma glucose (FPG) levels for 10–12 years prior to diagnosis of T2D.¹² This trajectory changes dramatically two years before diagnosis, reflecting acute beta-cell decompensation (Figure 1).

A continuum of stages of beta-cell dysfunction during progression to T2D have been described. Initial insulin hypersecretion to maintain normoglycaemia in the face of insulin resistance is followed by a stable state of beta-cell adaptation to a slightly elevated

Figure 1. Change in fasting plasma glucose prior to the onset of type 2 diabetes



glucose level with diminished glucose-stimulated insulin secretion (GSIS). Early decompensation leading to rapid elevation in glucose levels is then followed by a stable decompensation phase. Finally, there is severe decompensation representing profound beta-cell failure.¹³ Crucially, movement between stages 1 to 4 can be in either direction, highlighting the potential for regaining normal beta-cell function. Reducing demand on beta-cells (beta-cell rest) can improve insulin secretion and beta-cell viability.¹⁴

At diagnosis of T2D, 50% of beta-cell function has already been lost.¹⁵ Further loss is responsible for disease progression as the level of insulin resistance remains unchanged.¹⁶ Beta-cells are most metabolically stressed and vulnerable to apoptosis during the period of persistent hyperglycaemia around the time of the clinical onset of diabetes.¹² Restoration of normoglycaemia at this stage may protect beta-cell function for the long term.

Mechanisms of beta-cell damage: targets for reversal

Mechanisms for beta-cell dysfunction may include: glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, inflammatory stress and amyloid formation. These factors often act in concert and, without correction, lead to reduced functional beta-cell mass. It is unclear whether beta-cell failure results from reduced beta-cell number or function; a recent rodent study demonstrated beta-cell dedifferentiation under metabolic stress and conversion into other endocrine cell types including alpha cells with associated hyperglucagonaemia.¹⁷

Glucotoxicity

Chronic exposure to hyperglycaemia impairs GSIS and insulin biosynthesis.¹⁸ As hyperglycaemia causes oxidative and ER stress, beta-cell desensitisation and exhaustion ensue, leading to irreversible damage (beta-cell glucotoxicity) and apoptosis.¹⁹ These deleterious effects can be reversed by attaining normoglycaemia: insulin secretion increases in cultured beta-cells when media con-

taining supraphysiological glucose levels is switched to normoglycaemic media, reflecting recovery following relief of beta-cell exhaustion.²⁰ The efficacy of this intervention hinges on achieving normoglycaemia before beta-cell apoptosis occurs – it is time-dependent.

Lipotoxicity

Hypertriglyceridaemia increases peripheral insulin resistance, indirectly increasing beta-cell demand. The direct effect of prolonged islet exposure to free fatty acids is evidenced by impaired insulin gene expression and GSIS21 and beta-cell apoptosis.²² Lipotoxicity seldom occurs without hyperglycaemia: hyperglycaemia influences intracellular fatty acid metabolism, promoting the synthesis of cellular lipids which inhibit GSIS and insulin gene expression.²³ The term 'glucolipotoxicity' describes the synergistic deleterious effects on the beta-cell.

Oxidative and endoplasmic reticulum (ER) stress

Deteriorating metabolic control results in beta-cell oxidative and ER stress.²⁴ Beta-cells have low intrinsic antioxidant capacity, making them vulnerable to oxidative stress which then impairs insulin biosynthesis and secretion.^{25,26} Increased markers of oxidative stress are seen in serum and islets of individuals with T2D, and levels inversely correlate with the degree of insulin secretion.²⁷ Although controversial, antioxidants may improve GSIS in IGT and T2D.^{28,29}

The ER in the beta-cell is the critical cellular compartment for insulin biosynthesis. ER stress occurs when accumulation of abnormal proinsulin triggers the unfolded protein response signalling cascade.³⁰ This promotes beta-cell secretory dysfunction and, with chronicity, beta-cell apoptosis.³¹ Post-mortem pancreatic sections from patients with T2D show increased expression of genes associated with ER stress.³¹ ER size, a marker of ER stress, is twice as large in beta-cells from T2D patients compared with non-diabetic patients.³²

Inflammation

Pancreatic islets from individuals with T2D are infiltrated with immune cells and have elevated levels of pro-inflammatory cytokines.^{33,34} Transcription factor NF- κ B and pro-inflammatory cytokine interleukin (IL)-1 β are both activated by hyperglycaemia and hyperlipidaemia and are associated with impaired beta-cell function.^{35,36} Treatment with anakinra, an IL-1 β receptor antagonist, improved beta-cell secretory capacity in individuals with T2D.³⁷

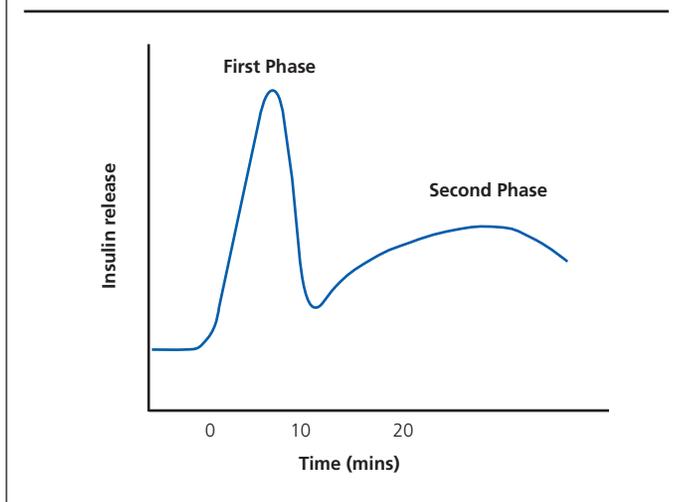
Amyloid deposition

Islet amyloid polypeptide (IAPP) aggregates to form pathological islet amyloid in T2D causing beta-cell dysfunction and death.³⁸ In chronic hyperglycaemia and hyperlipidaemia, IAPP synthesis increases in parallel with insulin synthesis, and can reach threshold levels that allow formation of pro-apoptotic IAPP oligomers.³⁹

First-phase insulin release

The normal insulin secretory response to glucose has a biphasic pattern (Figure 2). The first-phase response, essential in transitioning from fasting to fed states, suppresses postprandial hepatic glucose

Figure 2. Schematic of the first and second phase insulin release from the beta-cell in response to hyperglycaemia



production and peripheral lipolysis.⁴⁰ Within the beta-cell there are two functionally distinct pools of insulin secretory granules: a readily releasable pool containing 5% of the granules which accounts for first-phase secretion and a reserve pool containing the remaining 95% of granules accounting for the second phase.⁴⁰

Beta-cell dysfunction in T2D

Attenuation of first-phase insulin secretion is the earliest detectable defect in beta-cell function. It can be seen in patients with IGT,⁴¹ in normoglycaemic women with a history of gestational diabetes⁴² and in normoglycaemic first-degree relatives of patients with T2D.⁴³ The magnitude of first-phase insulin release inversely correlates with the degree of beta-cell dysfunction. The transition from normal glucose tolerance to T2D is associated with progressive deterioration in first-phase insulin secretion.¹⁰

Impaired first-phase release leads to postprandial hyperglycaemia (PPH) and increased risk of micro- and macrovascular complications.⁴⁴ Restoration of prandial insulin, with subcutaneous insulin analogues, improves glucose tolerance in T2D.⁴⁵ With diminished first-phase insulin secretion, plasma glucose rises causing beta-cell desensitisation and an augmented and sustained second-phase insulin release, characteristic of T2D.⁴⁶

Insulin deficiency

Longitudinal cohort studies have shown a gradual reduction in circulating insulin despite persisting insulin resistance.¹⁵ Initially this may be masked by excess production of proinsulins.⁴⁷ The rise in proinsulin represents increased insulin demand in T2D, causing depletion of mature insulin-rich granules with mobilisation of immature granules rich in proinsulin.

Beta-cell apoptosis

Post-mortem studies have shown that beta-cell number is reduced by 40% in patients with impaired fasting glucose (IFG) and 60% in T2D.⁴⁸ Beta-cell mass decreases with duration of diabetes due to the

increased rate of beta-cell apoptosis exceeding that of islet neogenesis and beta-cell replication – which remain relatively constant.⁴⁸

Loss of first-phase insulin response and cardiovascular (CV) risk

PPH is associated with an increased incidence of CV and all-cause mortality, even in individuals without T2D.^{44,49} Interventions that preserve beta-cell function and restore first-phase response – thereby attenuating PPH – theoretically could reduce CV events, although this has yet to be convincingly demonstrated in randomised controlled trials.

The HEART2D study found targeting PPH versus basal glucose in T2D after an acute myocardial infarction led to similar HbA_{1c} levels but no difference in the risk of CV events,⁵⁰ although post-hoc analyses suggested elderly patients may benefit.⁵¹ The NAVIGATOR study showed that, among patients with IGT plus CVD (or high risk for CVD), five years treatment with nateglinide to target PPH did not reduce CV events.⁵² The exception to these negative intervention studies has been the STOP-NIDDM trial in individuals with IGT: treatment with acarbose (α -glucosidase inhibitor that reduces PPH) led to a 49% risk reduction in CV events.⁵³

The UK Prospective Diabetes Study (UKPDS) showed a near linear relationship between HbA_{1c} and macrovascular disease, but this trial targeted FPG rather than PPH.⁵⁴ Conversely, the ORIGIN trial, using insulin glargine to target normal FPG for 6 years in people with early T2D or prediabetes (IFG or IGT) and a high risk of CV events, found that fasting normoglycaemia did not affect CV outcomes.⁵⁵

Early intervention and the 'legacy effect'

The UKPDS proved that glucose-lowering therapy with sulfonylureas or insulin lowered the risk of microvascular complications compared with dietary therapy.⁵⁴ During the 10-year post-trial monitoring period there emerged significant risk reductions in myocardial infarction and all-cause mortality, despite no persisting difference in HbA_{1c} or glucose-lowering therapy between the groups.⁷ This persisting benefit, beyond the period of intensive intervention in early T2D, is the 'legacy effect'.

The Steno-2 study involved a multifactorial risk reduction programme in relatively young patients with T2D, of whom 25% were not taking diabetes medication at baseline. After 7.8 years, HbA_{1c} was 7.9% in the intervention arm and 9.0% in the control arm. The control group were then offered treatment intensification. After a further 5.5 years of follow-up, no difference in glycaemic control or other cardiovascular risk factors remained between the intensive and control arms. Even so, over 13.3 years of follow-up the intensively treated group had an absolute risk reduction of mortality of 20% (HR 0.54, 95% CI 0.32 to 0.89; $p=0.02$) compared with conventional therapy.⁵⁶

Effect of later intensification

Tight glycaemic control achieved only later may be disadvantageous. In three large randomised controlled studies, despite improved glycaemic control with intensive therapy, benefits in macrovascular events were not seen.^{57–59}

In the ACCORD study, intensive therapy for 3.7 years increased mortality (HR 1.22, 95% CI 1.01 to 1.46; $p=0.04$) and did not reduce the incidence of major CV events.⁵⁸ A five-year follow-up of intensive therapy suggested a reduced risk for the combined coronary endpoints of myocardial infarction, coronary revascularisation and unstable angina,⁶⁰ but this was offset by the earlier increased CV mortality.⁶¹ Nine-year follow-up data show a neutral overall effect on death and non-fatal CV events, but the increase in CV-related death, observed on earlier analyses, persists.⁶²

In the VADT study, after 5.6 years of follow-up intensive glucose control in patients with poorly controlled T2D had no effect on the rates of CV events or death.⁵⁷

The ADVANCE study tested whether lowering HbA_{1c} to 6.5%, using gliclazide plus other drugs, improved microvascular and macrovascular outcomes. After five years a 10% relative reduction was seen in combined major macrovascular and microvascular events, primarily due to a 21% relative reduction in nephropathy.⁵⁹ After a further 5.4 years of follow-up from the end of the trial there was no legacy effect on macrovascular events.⁶³

More prolonged follow-up may possibly be required to observe a legacy effect. Alternatively, patient characteristics may be responsible. In the UKPDS trial, patients were older (60–66 years), had a longer duration of diabetes (8–11.5 years) and greater macrovascular disease burden (30–46%) than the younger, newly diagnosed patients. Benefits of intensive glycaemic control on macrovascular disease may only be seen if initiated early in the course of T2D.⁵⁷ It remains to be proven whether early recovery of first-phase insulin release is a component of macrovascular event reduction in these patients.

Glycaemic remission

Attainment of normoglycaemia, even if transient, shortly after diagnosis of T2D, may re-establish physiological beta-cell function and diet responsiveness for several years.³ Such an approach to the management of T2D avoids the glycaemic variability characteristic of the failing beta-cell as well as side-effects of chronic hypoglycaemic therapy or exogenous insulin such as weight gain and hypoglycaemia – themselves independent risk factors for CV disease.

Loss of first-phase insulin secretion is one of the earliest features of T2D and is associated with increased macrovascular disease risk and deteriorating beta-cell function. Early tight glycaemic control is an attractive prospect to mitigate or reverse these effects, although the evidence for clinical benefit remains uncertain.

Effect of current glucose-lowering therapies on beta-cell preservation

The management of T2D generally involves the progressive introduction of dietary and drug therapies to achieve normoglycaemia. Below we will discuss the evidence for beta-cell preservation of current glucose-lowering therapies, with particular reference to their effect on restoring first-phase insulin release when initiated at the time of diagnosis of T2D. It can be difficult to disentangle the effects of treatments on insulin resistance from those on beta-cell function. Some clinical studies have addressed this by a period of normoglycaemia prior to assessment of beta-cell function or by

correcting improvements in beta-cell parameters for improvements in insulin sensitivity.

Very low calorie diet (VLCD)

The effects of VLCD (<800 kcal/day) on T2D were first reported in the 1980s but have recently gained prominence with the potential for T2D remission.^{4,64}

VLCD leads to a reduction in fasting plasma glucose within the first days – when weight loss is minimal – largely attributable to reduced hepatic glucose output.^{4,65} This is associated with reduced basal insulin secretion, suggesting improved hepatic insulin sensitivity.^{4,65} It would be predicted that reduction in FPG would improve beta-cell function by amelioration of glucotoxicity and, in overweight patients with T2D, eight weeks of VLCD can lead to a gradual restoration of first-phase insulin response.^{4,66}

Reduced lipotoxicity following VLCD may also improve beta-cell function. A reduction in circulating free fatty acids (FFAs) and pancreatic triacylglycerol content has been observed with VLCD.^{4,66} Restoration of first-phase insulin secretion has been associated with reduced pancreatic fat, but no clear threshold exists relating pancreatic fat content to indices of insulin secretion, suggesting inter-individual variance to 'tolerance' of pancreatic fat.⁴ The detrimental effect of pancreatic fat may be mediated by a threshold level of toxic metabolites rather than a dose response effect of stored triglycerides.⁴

VLCD for 4–8 weeks in obese individuals with T2D resulted in sustained improvements in glycaemia at 12–18 months, even in patients who regained body weight (although a less marked effect was evident in those with weight regain).^{67,68} Normoglycaemia was partly attributable to increased beta-cell insulin secretion in response to an oral glucose tolerance test (OGTT).⁶⁸ Less durable effects have also been reported, with deterioration in glycaemic control within 12 months of VLCD.^{64,69} Baseline participant characteristics were similar between these studies, although the accompanying behavioural therapy programme varied.

Efficacy of VLCD is partly attributable to duration of T2D. VLCD for eight weeks achieved normoglycaemia (without other antidiabetic therapies) in 87% of individuals with a duration of diabetes <4 years compared with 50% of individuals with a longer duration of diabetes (>8 years).⁷⁰ Other characteristics predicting a favourable response to VLCD were younger age, lower baseline FPG and higher fasting and first-phase insulin levels at diet initiation. These may reflect the importance of having salvageable beta-cell function at dietary onset.⁷¹

The optimal duration and timing of VLCD in T2D is unknown. The relative efficacy of VLCD in early T2D compared with other proposed beta-cell preserving therapies such as early IIT warrants study.

Exercise

The effect of exercise in improving glycaemia in individuals with T2D is well established, even without weight loss.⁷² However, the effect of exercise on restoring beta-cell function is less well understood. Studies have shown that exercise therapy for 12 weeks shortly after diagnosis improves insulin sensitivity and increases early insulin secretion in response to OGTT in overweight individuals with

both IGT and T2D.⁷³ The increased early insulin secretion remains significant even when corrected for improvements in insulin sensitivity observed after the intervention in those with T2D.⁷⁴

In one study the beneficial effects of exercise training on beta-cell insulin secretion were only seen in individuals with T2D who had at least moderate beta-cell secretory capacity at baseline, suggesting an optimal timing of intervention.⁷⁵ Furthermore, exercise programmes were not able to normalise beta-cell function alone and many studies have combined exercise programmes with dietary interventions.

Metformin

Metformin inhibits hepatic glucose production and increases peripheral insulin sensitivity. In vitro studies suggest a directly protective effect of metformin on rat and human islets from glucotoxicity and lipotoxicity.^{76,77} In the UKPDS, patients with newly diagnosed T2D who received metformin had an initial increase in beta-cell function (assessed by HOMA) in the first year, but this subsequently declined at a similar rate to those treated with diet or sulphonylureas despite persistently increased insulin sensitivity with metformin.¹⁵ Similarly, the ADOPT (A Diabetes Outcome Progression Trial) study of recently diagnosed T2D patients showed a small early benefit of metformin on beta-cell function (in response to OGTT), followed by a slow decline – albeit less than those receiving sulphonylurea therapy – over four years.⁷⁸ Conversely, a recent study comparing 24 weeks of metformin to acarbose in overweight/obese Chinese patients with newly diagnosed T2D showed no significant effect of metformin therapy on early-phase insulin secretion following a mixed meal test.⁷⁹

Sulphonylureas

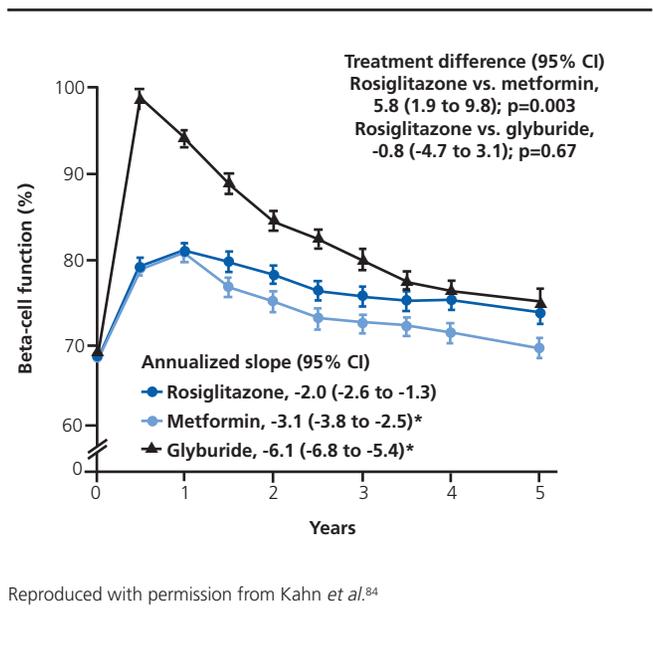
Sulphonylureas stimulate insulin secretion by inhibiting the ATP-sensitive potassium channel which, following beta-cell depolarisation, results in exocytosis of insulin-containing granules.⁸⁰ Some sulphonylureas – but not others – have been shown to acutely increase the first-phase insulin response to glucose in hyperglycaemic clamp studies in individuals with T2D.^{81,82}

In vitro studies of isolated human islets suggest that prolonged use of sulphonylureas may be toxic to beta-cells by inducing beta-cell apoptosis and loss of beta-cell mass.⁸³ Clinical trials including UKPDS and ADOPT showed that sulphonylureas initially increase early-phase insulin secretion in response to OGTT, but then lead to a more rapid rate of deterioration in this measure of beta-cell function and overall glycaemic control than treatment with metformin, thiazolidinediones or insulin therapy (Figure 3).^{15,78,84} These studies highlight the concept of beta-cell ‘rest’ to preserve long-term islet function.

Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-gamma (PPAR γ) agonists that regulate transcription of genes involved in lipid and glucose metabolism. The PPAR γ receptor is primarily expressed in adipose tissue, but also in pancreatic islet cells.⁸⁵ TZDs inhibit gluconeogenesis and enhance insulin sensitivity resulting in reduced fasting and postprandial glucose.⁸⁶ TZDs also

Figure 3. Beta-cell function (determined by HOMA 2) over time, according to treatment group (rosiglitazone, metformin or glyburide monotherapy)



promote FFA uptake and storage in adipose tissue and reduce FFA release from adipocytes by enhancing the antilipolytic effect of insulin.⁸⁷

TZDs also have direct effects on beta-cells. Incubation of human islet cells with rosiglitazone prevented FFA-induced downregulation of insulin mRNA expression and restored islet insulin content and glucose-stimulated insulin release. This effect was associated with reduced intracellular levels of toxic lipid metabolites.⁸⁸ TZDs also up-regulate expression of genes involved in beta-cell glucose sensing, including GLUT2 and glucokinase, leading to increased beta-cell sensitivity to glucose and improved insulin secretory capacity following OGTT, even after correction of improved insulin resistance.^{89,90}

TZDs can restore first-phase insulin response and improve other markers of beta-cell function, an effect independent of the correction of glucotoxicity.⁹¹ Preservation of beta-cell function, in addition to insulin-sensitising effects, means that TZDs can slow progression of IGT to T2D by 50–75% in high-risk individuals.^{92–94} Patients protected from diabetes with TZD therapy had stable beta-cell function and stable insulin resistance for up to five years.⁹⁵ The durability of effect of TZDs on beta-cell function in T2D is not clear; longer term studies of TZDs indicate that improvements in beta-cell function are sustained over two years in individuals with T2D uncontrolled with metformin or sulphonylurea monotherapy.⁹⁶ In the ADOPT study, rosiglitazone was associated with the lowest incidence of treatment failure in recently diagnosed T2D compared with sulphonylureas and metformin.⁷⁸

SGLT-2 inhibitors

Sodium glucose co-transporter 2 (SGLT-2) inhibitors block renal

glucose reabsorption, leading to increased urinary glucose excretion and lower plasma glucose.⁹⁷ SGLT-2 inhibitors have been shown to exert protective effects on beta-cell function (increased GSIS) and mass in obese T2D db/db mice,^{98,99} an effect likely mediated by reduced beta-cell glucotoxicity. Improvements in beta-cell function have been reported with SGLT-2 treatment; canagliflozin use for six months improved HOMA-B.¹⁰⁰ As SGLT-2 transporters are not present in beta-cells, the beneficial effects on function are unlikely to be direct beta-cell effects but secondary to improved glycaemic control, alleviating glucotoxicity.

Interestingly, SGLT-2 is expressed in pancreatic α -cells and treatment with dapagliflozin increases glucagon secretion in human islets and in healthy mice,¹⁰¹ an effect which has been reported in clinical studies in individuals with T2D and leads to enhanced endogenous glucose production despite reduced fasting plasma glucose.¹⁰²

GLP-1 receptor agonists and DPP-4 inhibitors

GLP-1 is an incretin hormone secreted in the distal ileum and colon in response to nutrient stimulation. Blunted GLP-1 secretion is seen in patients with T2D; however, GLP-1 receptors remain responsive to exogenous GLP-1.¹⁰³ In addition to potentiating GSIS, GLP-1 slows gastric emptying, inhibits α -cell glucagon secretion and reduces food intake.¹⁰⁴ GLP-1 has a very short half-life, rapidly inactivated by dipeptidyl peptidase 4 (DPP-4). DPP-4 resistant GLP-1 agonists and DPP-4 inhibitors are licensed for the treatment of T2D.

GLP-1 promotes insulin mRNA expression within the beta-cell, leading to maintenance of intracellular insulin stores and improved beta-cell secretory capacity.¹⁰⁵ GLP-1 also upregulates the biosynthesis of glucokinase and GLUT2, improving the capacity of beta-cells to sense and respond to glucose.¹⁰⁶ Studies of animal models of T2D and studies of human islets suggest that GLP-1 agonists increase islet cell replication and inhibit apoptosis, resulting in increased beta-cell mass.^{107,108}

Treatment with either GLP-1 agonists or DPP-4 inhibitors, as monotherapy or in combination with other agents, can restore the

first-phase insulin response.^{109–112} In the Liraglutide and the Preservation of Pancreatic β -Cell Function in Early Type 2 Diabetes (LIBRA) trial, following elimination of glucotoxicity with four weeks of IIT, treatment with liraglutide for 48 weeks led to further improvement in baseline adjusted insulin secretion to OGTT in patients with T2D.¹¹³

In animal studies, the protective effects of liraglutide on beta-cell function were more pronounced in the early stages of T2D than in the advanced stages.¹¹⁴ This reflects clinical studies in which the effect size of GLP-1 agonists on glycaemic control correlates with duration of T2D.¹¹⁵

Uncertainty remains regarding the optimal duration of treatment and durability of effect. Following cessation of GLP-1 treatment after one year (when improvements in beta-cell function were evident), the benefit was lost within weeks as beta-cell function returned to pre-treatment values.¹¹³ In contrast, individuals treated with exenatide for three years had sustained improvement in beta-cell function after a four-week washout compared with those receiving three years of insulin.¹¹⁶

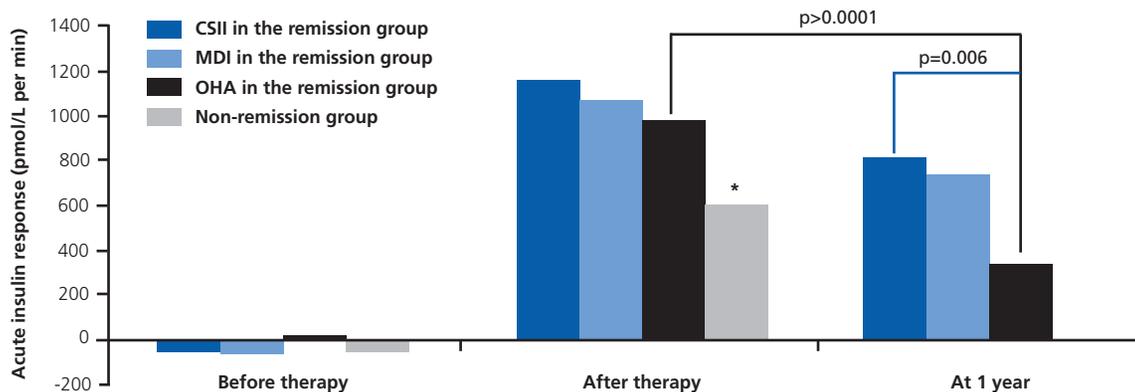
Early intensive insulin therapy (IIT)

Reducing beta-cell demand with short-term IIT might allow chronically overstimulated beta-cells to replenish the secretable insulin pool and improve beta-cell viability, thereby inducing long-term glycaemic control.^{3,117} Treatment with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDII) for two weeks achieved normoglycaemia in 95–97% of newly diagnosed patients with T2D.¹¹⁷ Normoglycaemia was maintained at one year in 44–51% of individuals (despite no additional antidiabetic therapy) compared with 27% initially treated with OHAs.¹¹⁷ The effect may persist for over two years.^{3,118}

The effect of short-term IIT early in T2D was to improve beta-cell function (first-phase insulin response, HOMA-B and proinsulin:insulin ratio).^{3,117,119} Restoration of first-phase insulin secretion predicted maintenance of euglycaemia at one year.³

What were the characteristics of the responders to IIT? These

Figure 4. Acute insulin response before and after different interventions and at 1 year



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individuals had a higher body mass index and lower FPG at baseline – possibly reflecting an intrinsic hyperinsulinaemic state.¹²⁰ They also had better initial glycaemic control, shorter duration of diabetes, with fewer diabetic complications and earlier attainment of glycaemic targets following initiation of IIT.^{121,122} These factors suggest that individuals with relatively preserved beta-cell function at treatment onset respond better to IIT.

Amelioration of glucotoxicity is unlikely to be the sole cause for improved beta-cell function with IIT. Short-term IIT (MDII or CSII) and oral hypoglycaemic agents (gliclazide and/or metformin) can both achieve high rates of initial euglycaemia, but IIT leads to significantly higher rates of remission and preservation of first-phase insulin secretion after one year than oral hypoglycaemic agents (Figure 4).¹¹⁷ The anti-lipolytic, anti-inflammatory and anti-apoptotic properties of insulin may also contribute to this.^{123,124}

Early introduction of short-term IIT has the potential to be a disease-modifying therapeutic option. The optimal approach for its implementation in clinical practice remains to be determined.

Bariatric surgery

Glycaemic control improves within several days following Roux-en-Y gastric bypass surgery (RYGB) in individuals with T2D.¹²⁵ Improvement in first-phase insulin secretion to an intravenous glucose tolerance test (IV GTT) occurs as early as one week after surgery, before significant changes in peripheral insulin sensitivity or weight have occurred.¹²⁶ Dramatically reduced nutritional intake may lead to improved beta-cell function due to relief of glucotoxicity as a similar pattern of early improved hepatic insulin sensitivity is seen following energy restriction.⁴ Obese patients with T2D who underwent RYGB or 500 kcal/day diet lost equivalent weight over three weeks and showed similar improvements in acute insulin secretion and beta-cell function in an IV GTT.⁶⁵

Postprandial GLP-1 secretion is substantially and durably increased early after RYGB, before significant weight loss has occurred, due to increased delivery of nutrients to the distal small intestine.¹²⁷ The importance of the incretin effect is unclear, with some studies showing that GLP-1 receptor blockade abolishes the RYGB-related improvement in beta-cell glucose sensitivity and insulin secretion¹²⁷ while another study found only minimal impairment in glucose tolerance following GLP-1 blockade after RYGB.¹²⁸

The durability of the effect of bariatric surgery on glycaemic control has been observed in the Swedish Obese Subjects Study; 72% of individuals with T2D achieved remission two years after surgery and 36% had maintained T2D remission 10 years after surgery.¹²⁹ Meta-analysis data report that 62% of patients with T2D remained free of diabetes for more than two years following surgery.¹³⁰

Identifying the characteristics of patients likely to obtain the greatest benefit from surgery is critical. Several factors are associated with failure of glycaemic control: longer duration of T2D, more severe diabetes requiring insulin therapy before surgery, older age and inadequate postoperative weight loss.¹³¹ Many of these characteristics have been noted throughout this review as important predictors of success or failure of dietary or pharmacological treatment of T2D.



Key messages

- Type 2 diabetes (T2D) is associated with progressive decline in beta-cell function with loss of first phase insulin response
- Loss of first phase insulin response is associated with increased cardiovascular risk
- Early intensive glycaemic control is associated with improved long-term morbidity and mortality
- Remission of T2D seen with very low calorie diet, intensive insulin therapy and bariatric surgery is associated with improved beta-cell function
- The greatest clinical benefit is observed when these interventions are delivered early in the course of T2D

Conclusions

With the potential for remission of diabetes seen with VLCD, early IIT and bariatric surgery, the focus of current treatment strategies needs to be revised. Interventions that preserve beta-cell function have improved durability on glycaemic control. It is not clear which intervention is most effective in achieving remission. However, the studies reviewed here suggest that several treatment options exist which, if delivered early enough in the course of T2D when beta-cell dysfunction is reversible, have the potential to preserve beta-cell function in the short and long term. Such interventions delivered after profound beta-cell failure has occurred are unlikely to be able to achieve remission of T2D. Aggressive treatment following diagnosis of T2D resulting in significant treatment-free periods is an attractive option. Comparative studies of different interventions in individuals with newly diagnosed T2D would be valuable to guide treatment recommendations.

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