E-Da Medical Journal 2022;9(2):21-37

Review Article

DOI: 10.6966/EDMJ.202206_9(2).0003

Clinical Approaches to Preserving β-Cell Mass and Function in the Management of Type 2 Diabetes

Kuo-Bin Tseng

Type 2 diabetes (T2D) is a chronic disease characterized by insulin resistance (IR) and impaired insulin secretion by β-cells, leading to persistent hyperglycemia. T2D is essentially caused by a progressive decline in β-cell mass and function. Disruption in the balance between β-cell growth and death may result in rapid and marked changes in β-cell mass. In autopsy studies, patients with T2D showed a 40% – 60% reduction in β-cell mass despite a normal capacity of β-cell neogenesis and replication. The observation that the degree of β-cell dysfunction is associated with a combination of metabolic, genetic, and environmental factors highlights the necessity of better understanding β-cell dysfunction in T2D development. These factors include glucolipotoxicity, cholesterol accumulation, islet amyloid deposition, inflammation, autoimmunity, incretins, and IR. The goal of T2D treatment is to not only reduce the glucose concentration but also prevent progressive decline in β-cells and delay disease progression. Therefore, developing new therapeutic strategies to preserve β-cells has become central in the management of T2D. This review presents the evidence on the efficacy of currently available clinical approaches to preserve β-cells in the management of T2D.

Key words: β-cell function, β-cell mass, type 2 diabetes, clinical approaches

Introduction

Diabetes represents a continuous spectrum of diseases with immune system involvement, wherein the destruction of β-cells in childhood is observed at one end and the age-related deterioration of metabolism lies at the other end.[1] Type 2 diabetes (T2D) is a complex and heterogeneous disease characterized by a reduction in β-cell mass and function and accompanied by varying degrees of insulin resistance (IR) in most cases. The pancreas initially responds to compensate for the increased metabolic demand by expanding β-cell mass and increasing insulin secretion in patients with T2D.[2] However, over time, when β-cells become refractory to increased blood glucose concentrations, relative insulin deficiency develops, resulting in reduced β-cell mass and dysfunction.[2]

Many factors affect insulin sensitiv-

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Cancer Hospital/I-Shou University, Kaohsiung, Taiwan.
Received: December 21, 2020 Accepted: January 28, 2021
Address reprint request and correspondence to: Kuo-Bin Tseng, Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Cancer Hospital, No.21, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan.
Tel: +886-7-615-0011 ext. 251876, E-mail: tsengkuobin@gmail.com

ity, including disordered insulin secretion, adipokines, inflammation, nutrients (glucose and lipids), and aging.[3] Some autopsy studies have reported that patients with T2D showed a 40% – 60% deficit in β-cell mass compared with individuals without diabetes.[2,4] Moreover, these β-cells are not only few in number but also exhibit disordered insulin secretion ability. Therefore, developing new strategies to increase β-cell mass and improve β-cell function can be a crucial therapeutic goal in the management of T2D. This review outlines common defects in β-cell mass and function and presents current clinical approaches used for preserving β-cell mass and function in the management of T2D.

Potential mechanisms underlying reduced β-cell mass and function

The natural history of T2D highlights the role of IR, insulin deficiency, and impaired incretin effect.[5] β-cells initially respond to compensate for the increased metabolic demand by increasing insulin secretion. As a result, the insulin levels initially will increase. This increase in insulin secretion actually still represents a relative deficiency of insulin because β-cell function starts to deteriorate in the early course of the nature history of the disease.[5] The existence of β-cell impairment is a necessary and sufficient condition for the appearance of prediabetes and the onset of frank diabetes. At the onset of diabetes, insulin secretion no longer makes progress as the same speed as IR, there is already a significant reduction in β-cell function. By the time diabetes is clinically diagnosed, β-cell function may be reduced by ≥ 50%.[5] β-cell impairment are now recognized to arise and worsen years before the onset of diabetes and its initial manifestation of postprandial hyperglycemia. Moreover, whether as cause or consequence, the decline in incretin effect is clearly present in T2D.[5] Together these 3 core pathophysiologic defects likely combine to contribute to the progressive nature of the disease, and may account for much of the deterioration in glucose control observed clinically in patients with T2D.

T2D comprises an array of metabolic disorders characterized by hyperglycemia along with a combination of defects in insulin secretion and action as well as excessive or inappropriate glucagon secretion. Currently, most clinical therapeutic strategies for T2D treatment either aim to increase the insulin level by enhancing β-cell function or aim to reduce IR. Considering a potential exhaustive effect on β-cells, many basic studies have investigated mechanisms for preserving β-cell function and regenerating β-cell mass. Thus, a thorough understanding of the dynamics and contribution of β-cell function and mass to IR compensation and progression to T2D is necessary (Fig. 1).

β-cell mass

The constant flux of β-cell mass makes it adaptable to prevailing physiological needs. A change in β-cell mass appears to reflect the net dynamic processes of β-cell mass expansion through β-cell hypertrophy and replication as well as neogenesis from non-β-cell sources and β-cell loss through apoptosis or necrosis as well as β-cell dedifferentiation.[6] Disruption in any of these pathways of β-cell formation or increased rates of β-cell death can reduce β-cell mass.[2]

In patients with varying degrees of obesity and IR, the insulin output through expanded β-cell mass and enhanced secretion may neutralize the development of glucose intolerance and hyperglycemia.[7] Many studies have suggested that β-cell mass tends to be reduced in patients with T2D compared with healthy individuals. The total islet volume decreased by 30% in patients with diabetes compared with those without diabetes (0.41 ± 0.05 cm^3 vs. 1.58 ± 0.16 cm^3, respectively).[8] Findings from a large pool of pancreatic tissues from 124 human autopsies indicated that the relative β-cell volume and presump-

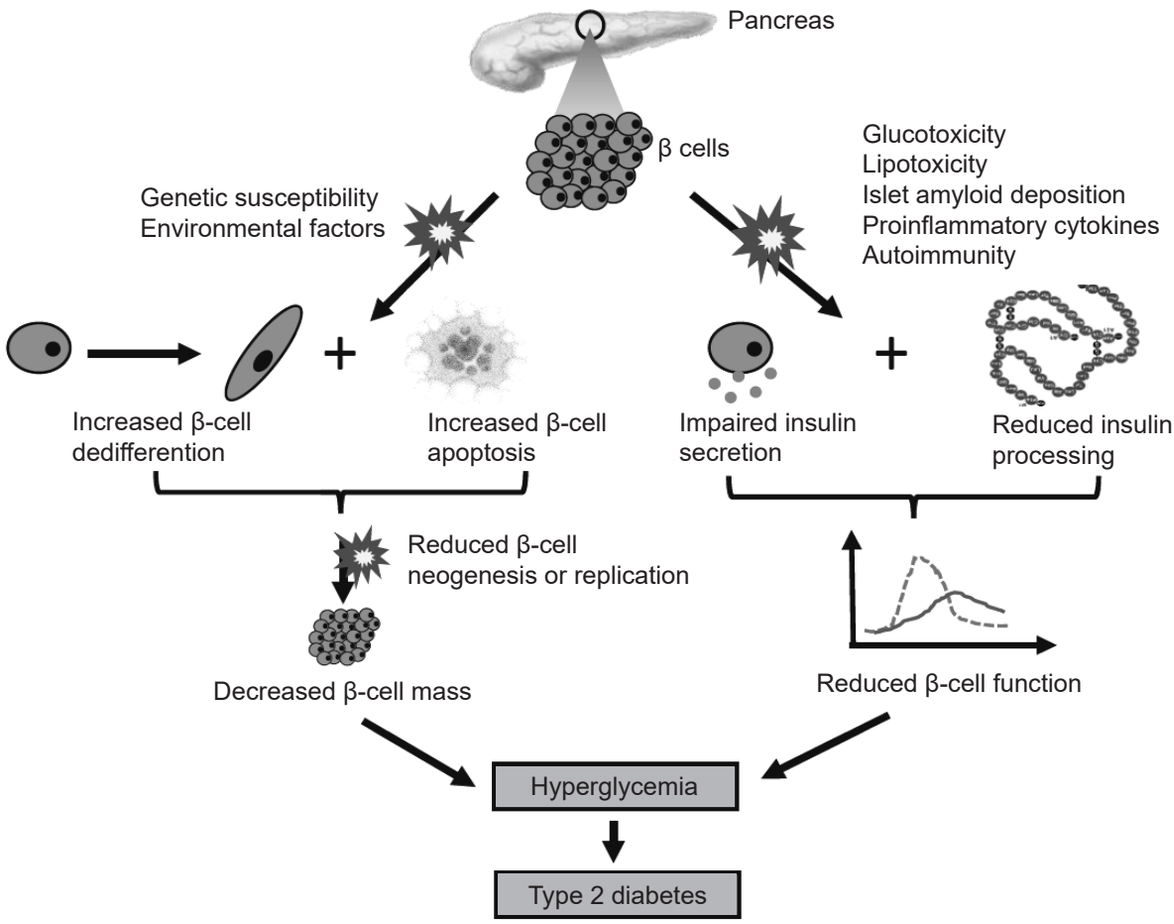

Fig. 1 The decline of β-cell mass and function is multifactorial. As a result, hyperglycemia can eventually lead to type 2 diabetes.

tive β-cell mass were reduced in both lean and obese patients with T2D compared with their age- and weight-matched counterparts without diabetes.[2] Furthermore, the reduction in β-cell mass was attributed to an increase in the frequency of β-cell apoptosis 10- and 3-fold in lean and obese patients with T2D, respectively, compared with their respective controls without diabetes; however, the rates of new islet formation and β-cell replication were unaffected.[2]

A morphometric analysis showed a 22% ($p < 0.001$) reduction in β-cell volume density and a 30% ($p < 0.05$) reduction in total β-cell mass in Japanese patients with T2D.[9] The relative β-cell volume in Korean patients with T2D was < 50% of that in body mass index (BMI)-matched normal individuals and was correlated significantly with their BMI.[10] Similarly, after BMI matching, β-cell mass was 41% (BMI < 25) and 38% (BMI = 26 – 40) lower in European patients with T2D than in individuals without T2D, irrespective of sex or treatment type.[4]

Taken together, most studies have identified a significant reduction in β-cell mass that ranges from 40% to 60% in patients with T2D, representing an unexpected broad heterogeneity of β-cell mass. The β-cell mass reduction in patients with T2D can most likely be attributed to a greatly increased rate of β-cell apoptosis and probably not to differences in β-cell replication frequency or neogenesis.[11] However, these human studies were not prospective in nature given that they were performed at autopsy. In addition, these studies did not rule out the possibility of a decreased inherent β-cell mass caused by genetic or environmental factors, which can be strong risk factors for

T2D. If this were the case, the reduced β-cell mass observed in patients with T2D would not necessarily be the sole consequence of the disease itself.

β-cell function

Many physiological stressors have a role in the decline of β-cell function in the environment of metabolic overload and IR. Although β-cells initially activate compensatory pathways to improve the insulin secretory response, they eventually initiate several pathological programs that synergistically promote β-cell dysfunction and apoptosis.[12] Hyperglycemia and glucose toxicity might activate the protein kinase C pathway, enhance the polyol pathway, increase oxidative stress (OS), and overproduce advanced glycation end products, all of which are potential cellular mechanisms resulting in β-cell dysfunction.[13,14] Similarly, lipotoxicity eventuates in β-cell dysfunction and apoptosis through endoplasmic reticulum (ER) stress, OS and mitochondrial dysfunction, impaired autophagy, and inflammation.[15]

The proinflammatory cytokine interleukin (IL)-1β can lead to β-cell dysfunction and promote Fas-triggered apoptosis, partly mediated by activating the nuclear transcription factor NF-κB.[16] Likewise, an increased ratio between IL-1β and IL-1 receptor antagonist through leptin released from fat depots can result in an increase in β-cell apoptosis and impaired glucose-stimulated insulin secretion in human islets.[17] Amyloid plaques result from the aggregation of the islet amyloid polypeptide (IAPP), which is synthesized and secreted by β-cells upon glucose stimulation, parallel to proinsulin. The presence of extracellular amyloid plaques adjacent to β-cells and intracellular toxic oligomers that consist of IAPP are associated with β-cell dysfunction.[18]

These postulated mechanisms and the timing of T2D onset at a given level of β-cell function loss may actually depend on the individual and are affected by stressors.[12] Elucidating the underlying mechanisms may be difficult; however, acquired and several genetic factors have been identified, together with the likely molecular cross-talk and convergence between pathways possibly involved. Novel insights into pathways activated within β-cells to cope with stress have been offered in recent studies, adding to the potential approaches to alter the natural history of T2D. Novel therapies that exploit these natural defense mechanisms to prevent or slow the decline of β-cell function in T2D may be possible.[12]

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

Treatments for β-cell dysfunction should strive to stimulate β-cell neogenesis and replication to enhance β-cell mass, reduce β-cell apoptosis, limit inflammatory mediators, and ameliorate the overproduction or inadequate clearance of amyloid plaques in islets. The identification of factors conferring susceptibility and those that may accelerate such processes may be a crucial therapeutic strategy for the preservation and restoration of β-cell mass and function in the primary prevention of T2D and for the reduction of the risk of long-term diabetic complications. Ideally, a therapeutic agent should prevent the gradual decline in β-cell mass and function, prompting increased insulin secretion at a specific insulin sensitivity (Table 1).

Lifestyle modifications

Caloric restriction might preserve β-cell function in patients with diabetes.[19,20] Caloric restriction was associated with reductions in fasting plasma glucose, hepatic glucose production, and fasting plasma triglyceride and increases in insulin sensitivity and secretion.[20] A study provided strong evidence of an exercise training-induced increase in β-cell function in response to intravenous glucose in patients with T2D and obesity.[19] However, the optimal and timing of caloric restriction in T2D remain

unknown. Exercise interventions in which more than 2,000 calories per week are expended increased β-cell function in a linear dose-response manner in adults with poor insulin secretion capacity.[21] However, exercise training alone could not normalize β-cell function, and many studies have combined exercise training with dietary interventions.

Lifestyle modifications could not only relieve underlying IR in obesity but also potentially reverse β-cell dysfunction in older patients with obesity and T2D.[22] This result highlights that lifestyle modifications may improve β-cell function through changes in intestinal incretin secretion in patients with T2D.[22] Future studies should compare the efficacy of lifestyle modifications in T2D with those of other proposed β-cell-preserving therapies, such as early intensive insulin therapy (IIT).

Metformin

Metformin is a widely used antidiabetic agent to treat T2D. Incubation of T2D islets for 24 hours with metformin resulted in increased insulin content and the number and density of mature insulin granules, improved glucose-induced insulin release with partial first-phase restoration, enhanced insulin mRNA expression, and reduced apoptosis.[23] Metformin exerts direct beneficial effects on β-cell functions, such as insulin release, transcriptional regulation in islets, and islet cell viability, being dependent on the presence of glucose.[24] The permeability transition pore (PTP) is a mitochondrial channel associated with cell death. Metformin prevents glucolipotoxicity-induced PTP opening in permeabilized and intact INS-1 cells (the rat insulinoma cell line) to preserve β-cell viability.[25] The β-cell protective activity of metformin in lipotoxicity was associated with the suppression of ER stress-induced apoptosis through the regulation of adenosine monophosphate-activated protein kinase/phosphatidylinositol-3 kinase activation and the c-Jun N-terminal kinase pathway.[26]

According to the findings of the Diabetes Prevention Program, metformin could preserve β-cell function by exerting combined beneficial effects on both insulin sensitivity and secretion in patients with impaired glucose intolerance (IGT).[27] A similar result was reported in a study that suggested that metformin halts the progressive deterioration of β-cell function in youth with IGT or recently diagnosed T2D.[28] In a mouse model of T2D, a combination of metformin with dipeptidyl peptidase (DPP)-4 inhibitors (DPP-4is) improved hyperglycemia and synergistically increased β-cell mass, these outcomes were believed to result from an increase in glucagon-like peptide-1 (GLP-1) secretion and DPP-4 inhibition.[29]

Although accumulated evidence has shed light on metformin action, the exact mechanism by which metformin protects β-cells remains unclear, warranting further investigations in the near future.

Sulfonylureas and glinides

Concern has been raised regarding the application of sulfonylureas (SUs) in T2D treatment that leads to the loss of β-cell mass and function because studies have demonstrated that agents that cause closure of the inwardly rectifying K+ sulfonylurea receptor subtype of adenosine triphosphate-sensitive potassium (KATP) channels induce β-cell apoptosis in human islets and may precipitate the decrease in β-cell mass observed in patients with T2D.[30] No β-cell apoptosis was found with a low concentration of glinide. However, at a high concentration, glinide induced a 1.49-fold increase in the number of apoptotic β-cells.[30] Moreover, prolonged 4-day exposure of islets to glinides induced β-cell apoptosis.[30] Similarly, the Prospective Diabetes Study conducted in the United Kingdom reported a progressive decline in β-cell function in patients receiving SU treatment.[31]

Different disturbances in islet cell

Table 1. Clinical approaches for preserving β-cell mass and function in type 2 diabetes.

Interventions	Mechanisms	Mode of action in β cell	β-cell mass	β-cell function
Lifestyle modifications	Decrease fasting plasm glucose, hepatic glucose production and fasting plasm triglyceride[20] Relieve insulin resistance in obesity[22] Change intestinal incretin secretion[22]	Increased insulin sensitivity and secretion[19-22]	None	Improved β-cell function[19-22]
Metformin	Decrease hepatic glucose production and increase insulin sensitive of body tissues by activating the cellular energy sensor AMP-activated protein kinase[23-29]	Increased insulin content and number and density of mature insulin granules[23] Improved insulin release with partial restoration of 1st phase insulin secretion[23] Preserved β-cell viability[25] Increase insulin sensitivity and insulin secretion[28] Halted the progressive deterioration of β-cell function[28]	When combined with dipeptidyl peptidase-4 inhibitors synergistically enhancedβ-cell mass[29]	Improved β-cell function[23,25,28]
Sulfonylureas and glinides	Inhibit potassium efflux (blocks KATP channels), causing depolarization & insulin release from β-cells[30-35]	Closure of the inwardly rectifying K+ sulfonylurea receptor subtype of KATP channels induces β-cell apoptosis[30] Impaired acute insulin secretion through reduction of the insulin content, reduction of the number of functional KATP channels on the plasma membrane, and accelerated β-cell apoptosis[33]	Decreased β-cell mass[30]	Aggravated β-cell function[30-33]
α-glucosidase inhibitors	Inhibit the enzyme α-glucosidase to delay the digestion of complex carbohydrate and intestinal absorption of glucose[36-39]	Altered carbohydrate digestion products from the colon to improve insulin sensitivity[37] Probably increase insulin sensitivity through decreased glucotoxicity[40] Affected β-cell function via increased GLP-1 release[43] No change in insulin sensitivity[41,42]	None	Controversial effects on β-cell function[36-39]
Thiazolidinediones	Activate PPAR-γto alter the transcription of several genes involved in glucose and lipid metabolism and energy balance[44-47]	Prevented β-cell apoptosis[44] Reduce lipotoxicity[45] Suppress tumor necrosis factor-α expression[46] Enhancedβ-cell sensitivity[50] Reversed lipotoxicity[50] Maintained β-cell proliferation and prevented net β-cell death[51] Restored 1st phase insulin response[52] Modulated oxidative stress, mitochondrial dysfunction, epigenetic dysregulation, and ER stress[54] Upregulated PDX-1 expression[57] Increase insulin gene transcription, GLUT2, and glucokinase[57]	Hampered β-cell mass loss[51]	Improved β-cell function[48-50,52]

Dipeptidyl peptidase-4 inhibitors	Enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon[63-73]	Anti-inflammatory effect[63] Decreased leukocyte telomere length and telomerase activity[65] Stabilized GLP-1[66] Increase insulin sensitivity[67] Ameliorated ER stress[58-62] Stimulated β-cell differentiation and proliferation and inhibited apoptosis[58-62]	Increased β-cell mass[58-62]	Improved β-cell function[58-62,64-66,74]
Glucagon-like peptide-1 receptor agonists	Stimulate glucose-dependent insulin release from β-cell, slow gastric emptying, inhibit inappropriate post-meal glucagon release[60,61,75]	Stimulated β-cell proliferation, increased β-cell neogenesis and inhibited β-cell apoptosis[60,61,75] Restore 1st and 2nd insulin secretion[76,79] Enhanced β-cell sensitivity[77,81] Improved HOMA-B, proinsulin/insulin ratio, and proinsulin/C-peptide ratio[80]	Increased β-cell mass[60,61,75]	Improved β-cell function[76,77,79,80]
Sodium glucose co-transporter 2 inhibitors	Inhibit SGLT2 in the proximal convoluted tubule, to prevent reabsorption of glucose and facilitate its excretion in urine[88-91]	Increased β-cell proliferation and decreased β-cell apoptosis[82] Decreased OS, ER stress, and inflammation gene expression[85] Increased the plasma C-peptide concentration curve[88] Augmented β-cell glucose sensitivity[89] Improved HOMA-B[91]	Increased β-cell mass[82,85]	Improved β-cell function[88-91]
Intensive insulin therapy	Facilitate entry of glucose into muscle, adipose and several other tissues[94-99]	Increased C-peptide concentrations and C-peptide response to glucagon[94] Improved insulin resistance[95,96] Improved the HOMA-B index, area-under-the-insulin-curve, and insulinogenic index[101]	None	Improved β-cell function[94-99,101]

AMP: adenosine monophosphate; GLP-1: glucagon-like peptide-1; KATP: adenosine triphosphate-sensitive potassium; mRNA: messenger ribonucleic acid; PPAR-γ: peroxisome proliferator-activated receptor-gamma; GLUT2: glucose transporter 2; ER: endoplasmic reticulum; HOMA-B: homeostatic model 2 assessment of β-cell function; OS: oxidative stress; SGLT2: sodium glucose co-transporter.

function and survival were observed with a prolonged exposure of cultured human islets to different SUs; milder effects were observed with glimepiride compared with glibenclamide and chlorpropamide.[32] Chronic exposure of β-cells to SUs and glinides was associated with the impairment of acute insulin secretion through a reduction in insulin content and the number of functional KATP channels on the plasma membrane and the acceleration of β-cell apoptosis.[33] A study indicated that gliclazide protects β-cells from apoptosis through antioxidant effects in T2D.[34]

Whether the loss of β-cell function reflects desensitization to SUs remains unclear. Sustained exposure of β-cells to SUs induced a reversible state of refractoriness to acute stimulation with SUs but not to other glinides in patients with T2D, probably through different mechanisms of action.[35] Although accumulated evidence has shed light on the action of SUs and glinides, the exact mechanisms through which SUs and glinides affect β-cell mass and function remain unclear. More studies are necessary to further elucidate the detailed mechanisms underlying the effects of SUs and glinides on β-cell mass and function.

α-glucosidase inhibitors

Inconsistent and controversial effects of α-glucosidase inhibitors (AGIs) on β-cell function have been observed. The effects of AGIs on β-cell function in response to a mixed meal have shown an increase,[36] no change,[37,38] or a decrease[39] in patients with diabetes. However, the causes of these inconsistent findings remain unclear In these studies, patients were older, their duration of therapy was short, the patient samples were small, diabetes was either fair or poorly controlled, and patients were treated simultaneously with other oral hypoglycemic agents (OHAs). Acarbose was proposed to reduce glucose levels that further result in a reduction in glucotoxicity, leading to increased insulin sensitivity.[40] Similarly, acarbose was reported to alter carbohydrate digestion products in the colon, such as fatty acids, which exerted an effect on insulin sensitivity.[37] However, studies of acarbose in patients with T2D have shown no change in insulin sensitivity despite significant reductions in glucose levels.[41,42] AGIs might affect β-cell function through increased GLP-1 release in patients with T2D.[43] Although the inconsistent effects of AGI-based medications maintain β-cell function, there is no evidence that they improve β-cell mass.

Thiazolidinediones

Thiazolidinediones (TZDs) prevent β-cell apoptosis,[44] reduce lipotoxicity,[45] suppress tumor necrosis factor-α expression,[46] and improve insulin response,[47] suggesting a protective role of TZDs in β-cells. Apart from the insulin-sensitizing action, TZDs exert a potent effect that preserves β-cell function[48,49] and demonstrate durable glycemic control for up to 5 years.[50] In addition, TZDs exert direct effects at the β-cell level. The incubation of human islet cells with TZDs restored islet insulin content and glucose-stimulated insulin release through the prevention of free fatty acid-induced downregulation of insulin mRNA expression.[45] This effect resulted from the activation of metabolic pathways that reduced the intracellular formation of toxic compounds.[45] Similar findings were reported in obese Zucker rats with diabetes, showing that TZDs hampered the loss of β-cell mass by maintaining β-cell proliferation and preventing net β-cell death.[51]

TZDs induced the recovery of β-cell function, as evidenced by the restoration of the first-phase insulin response and improvement in other makers of β-cell function. This effect was independent of the correction of glucotoxicity.[52] Treatment with TZDs in patients with a high risk of diabetes resulted in stable β-cell function and ameliorated IR for up to 5 years.[53] The protective effect of TZDs on

β-cell function is suggested to stimulate peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptors on β-cells, enhance β-cell sensitivity to glucose, and reverse lipotoxicity.[50] More recently, a novel TZD, lobeglitazone, showed beneficial effects on both β-cell function and survival by directly reducing β-cell apoptosis and increasing β-cell proliferation through the modulation of ER stress markers and cell survival markers.[54] However, apart from these direct protective effects of TZDs on β-cells, conflicting results have been obtained, especially in animal models of PPAR-γ ablation. TZDs restored insulin secretion in a total-body PPAR-γ deletion model[55] but not in a β-cell-specific PPAR-γ knockout model.[56]

Potential mechanisms underlying the direct beneficial effects of TZDs on β-cells have been proposed. PPAR-γ directly regulates key β-cell genes involved in glucose sensing, insulin secretion, and insulin transcription, including PDX-1, glucose transporter 2, and glucokinase.[57] The prosurvival effects of TZDs on β-cells are exerted by modulating OS, mitochondrial dysfunction, epigenetic dysregulation, and ER stress.[54] TZDs have also been suggested to protect against glucose-, lipid-, cytokine-, and islet amyloid polypeptide-induced activation of stress pathways.[57] These complementary profunctional and prosurvival effects of TZDs synergize to preserve β-cell mass and function in T2D.

DPP-4is

DPP-4is augment insulin secretion and increase β-cell mass by stimulating β-cell differentiation and proliferation and ameliorating ER stress, inflammation, and apoptosis in vitro and in animal models of T2D.[58-62] Similar beneficial effects were observed in patients with T2D; DPP-4is exerted an anti-inflammatory effect,[63] which may improve β-cell function and survival.[64] DPP-4is protected β-cells by reducing leukocyte telomere length and telomerase activity.[65] DPP-4is restored β-cell function and survival in human isolated islets through GLP-1 stabilization.[66] DPP-4is improved β-cell function and insulin sensitivity, leading to improved postprandial glycemia in patients with impaired fasting glucose.[67] DPP-4is may also improve fasting islet-cell function in patients with T2D.[68] In drug-naïve patients with T2D and mild hyperglycemia, DPP-4i monotherapy significantly reduced glycosylated hemoglobin (HbA1c) through improved β-cell function compared with a placebo.[69] More recently, a meta-analysis of data from 52 randomized controlled trials (RCTs) showed that DPP4is as monotherapy or as add-on therapy significantly improved β-cell function but exerted no significant effect on IR.[70]

Little evidence supports the sustained effects of DPP-4is on β-cell function in humans, although an RCT prolonged treatment for up to 2 years.[71] A systematic review evaluated glycemic durability with a DPP-4i as a surrogate marker of improvement in β-cell function, suggesting that the effect of DPP-4is on HbA1c decreased during the second year of treatment.[72] A meta-analysis of RCTs suggested that DPP-4is attenuated the further decline in β-cell function during the 2-year follow-up period when compared with a placebo, especially in patients not receiving any antidiabetic drug and with higher homeostatic model 2 assessment of β-cell function (HOMA-2β) at baseline.[73] Moreover, this study indicated that DPP-4is effectively prevent the progression of T2D, especially in the early stage of the disease.[73]

Whether DPP-4i monotherapy alters the progressive course of T2D by preserving functional β-cell mass in the presence of persistent damaging factors, such as glucolipotoxicity, OS, inflammation, and IR, remains unclear. Recently, results of the vildagliptin efficacy in combination with metformin for early treatment of type 2 diabetes (VERIFY) trial presented at 56th Virtual Annual Meeting of

European Association for the Study of Diabetes demonstrated that the early combination treatment with DPP-4i (vildagliptin) plus metformin in patients with newly diagnosed T2D (within 2 years) improved β-cell function compared with metformin monotherapy.[74] Therefore, DPP-4is may be particularly useful in the early stage of the disease when combined with agents addressing complementary pathophysiological mechanisms. Nevertheless, additional long-term studies are necessary to confirm that DPP-4is result in a durable improvement in islet-cell function and attenuate the progression of T2D by preserving β-cell function.[71]

Glucagon-like peptide-1 receptor agonists

Several preclinical models of T2D studies have shown that GLP-1 receptor agonists (GLP-1 RAs) can enhance β-cell mass, stimulate β-cell proliferation, increase β-cell neogenesis, and inhibit β-cell apoptosis.[60,61,75] Although the direct effects of GLP-1 RAs on β-cell mass have not yet been demonstrated in clinical studies due to the lack of a suitable noninvasive technology, their positive effects on islet cell function have consistently been reported.

Exenatide demonstrated significant improvements in the multiple indices of β-cell function, such as the proinsulin/insulin ratio and HOMA-β, in a placebo-controlled study.[76] Exenatide or exenatide with rosiglitazone showed a significant improvement in the first- and second-phase insulin secretion in a 20-week randomized open-label multicenter study involving patients with T2D who received metformin ($p < 0.05$).[77] Moreover, insulin sensitivity was significantly higher in exenatide treatment with rosiglitazone versus exenatide treatment alone ($p = 0.014$).[77] A similar beneficial effect was observed in patients with uncontrolled T2D who received therapy with metformin, suggesting that compared with glimepiride, exenatide was associated with a significant improvement in the HOMA-β index.[78]

A study examined the effects of different doses of liraglutide versus that of a placebo on β-cell function in patients with T2D and reported that liraglutide improved first- and second-phase insulin and arginine-stimulated insulin secretion during hyperglycemia.[79] In the Liraglutide Effect and Action in Diabetes (LEAD) trials, 1.2 and 1.8 mg of liraglutide significantly improved multiple indices of β-cell function versus a placebo, including the HOMA-β index, proinsulin/insulin ratio, and proinsulin/C-peptide ratio.[80] Liraglutide resulted in a 25% improvement in HOMA-β when combined with metformin and glimepiride.[80] Moreover, across all six LEAD studies, liraglutide demonstrated a 20% – 44% improvement from baseline in HOMA-β.[80] More recently, liraglutide was reported to significantly improve β-cell function without exerting an effect on α-cell function in patients with well-controlled T2D and coronary artery disease.[81] Moreover, when combined with metformin, liraglutide reduced the ambient insulin level and improved insulin sensitivity and clearance in a physiological meal test setting, suggesting that liraglutide can be used as a flexible insulinotropic drug in these patients.[81]

Although GLP-1 RAs demonstrated the beneficial effects of GLP-1 on β-cell function in clinical studies, uncertainty remains regarding the optimal duration of treatment and the durability of the effect. Additional studies are required to investigate whether GLP-1 RAs result in sustained improvements in β-cell mass and function over time in patients with T2D.

Sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors (SGLT2is) exert beneficial effects by preserving β-cell function in animal models.[82-87] Luseogliflozin exerted positive effects on β-cell function protection in obese T2D db/db mice through an effect likely mediated by ameliorated β-cell glucotoxicity.[82] β-Cell mass was

larger in luseogliflozin-treated mice, which was due to reduced β-cell apoptosis and increased β-cell proliferation.[82] Moreover, the expression levels of various β-cell-related factors, including insulin, and insulin gene transcription factors, such as MafA and PDX1, were significantly higher in luseogliflozin -treated mice.[82] Earlier and longer treatment with luseogliflozin increased the beneficial effects on β-cells observed in diabetic db/db mice.[83] Similar protective effects were observed in a diabetic mouse study; this study reported that empagliflozin preserved multiple β-cell-related factors, such as MafA and PDX1, insulin, glucose transporter 2, and the GLP-1 receptor.[84] Empagliflozin resulted in the augmentation of β-cell proliferation.[84] More recently, empagliflozin was suggested to protect β-cell mass against glucotoxicity through a reduction in OS, ER stress, and inflammatory gene expression in streptozotocin-treated mice.[85] Dapagliflozin sustained β-cell function and preserved the islet morphology in obese diabetic rats.[86] Dapagliflozin exerted beneficial effects on β-cells, reduced glucagon, and did not alter β-cell to α-cell transdifferentiation in diabetic mice.[87]

SGLT2is could improve β-cell function in patients with T2D.[88-91] The incremental area under the plasma C-peptide concentration curve tended to increase in patients with T2D receiving dapagliflozin treatment compared with those receiving a placebo during a 75-g oral glucose tolerance test (OGTT).[88] Treatment with empagliflozin in patients with T2D improved β-cell function and augmented β-cell glucose sensitivity, as measured using the insulin secretion/IR index during hyperglycemic clamp.[89] Furthermore, treatment with ipragliflozin significantly improved β-cell function in Japanese patients with T2D, as assessed using the OGTT-derived disposition index.[90] Similarly, canagliflozin resulted in an improvement in HOMA-β in patients with T2D.[91]

SGLT2 is also expressed in α-cells, and SGLT2i treatment facilitates glucagon secretion, which results in the augmentation of hepatic gluconeogenesis.[92] Moreover, glucagon gene expression was higher and SGLT2 expression was lower in islets from patients with T2D and in normal islets exposed to chronic hyperglycemia than in islets from individuals without diabetes.[92] Despite such an unexpected effect, SGLT2i treatment led to a lower blood glucose level compared with the placebo probably due to increased glycosuria; nevertheless, the resulting increase in the plasma glucagon level represented a possible concerning side effect, especially in a patient population already affected by hyperglucagonemia.[92]

Taken together, these studies suggest that SGLT2is are beneficial in preserving β-cell function. However, whether SGLT2is can enhance β-cell mass in patients with T2D remains unclear. Therefore, further investigation of the actions of SGLT2is is warranted to obtain a more complete understanding of their β-cell protection and many other clinically beneficial effects.

Intensive insulin therapy

IIT could reduce secretory requirements for β-cells to nearly zero. β-Cell "rest" may lead to the recovery of β-cell function and probably prevents a progressive decline in β-cell mass. However, whether such "rest" underlies recovery through the elimination of hyperglycemia and the involved glucotoxicity and lipotoxicity remains unclear. In addition, the observation that insulin receptors on β-cells mediate insulin synthesis and secretion leads makes the use of insulin as a remedy for the recovery of β-cell dysfunction possible.[93]

Numerous studies have investigated the effects of IIT on β-cell function and glycemic control.[94-99] A study assessed the effects of 3-week IIT on endogenous insulin secretion and action in patients with T2D, suggesting that continuous subcutaneous insulin infusion (CSII) increased the C-peptide concentration

by 28% ($p < 0.05$), and the response of the C peptide to glucagon was markedly enhanced.[94] Compared with OHA treatment, IIT showed more satisfactory effects on the recovery and maintenance of β-cell function and IR in patients with newly diagnosed T2D.[95,96] Moreover, the remission rate (off medication) in patients with newly diagnosed T2D receiving IIT was between 43.8% and 47.1% after 1 year.[97,98]

A multicenter randomized trial demonstrated that the rapid correction of hyperglycemia improved β-cell function after 2-week intensive therapy in patients with newly diagnosed T2D, irrespective of treatment with insulin (CSII or multiple daily insulin injections [MDIs]) or OHAs.[96] Moreover, the remission rate (off medication) after 1 year was significantly higher in the insulin group (51.1% in CSII and 44.9% in MDI) than in the OHA group (26.7%; $p = 0.0012$). The remission rate was slightly higher in the metformin group than in the gliclazide group. However, no conclusion could be drawn because only a small proportion of patients was included in each group. In all patients in the remission group, improvement in the acute insulin response was sustained with insulin but significantly reduced in those treated with OHAs.[96] A similar result was reported in patients with newly diagnosed T2D and severe hyperglycemia treated with short-term IIT, suggesting that early insulin therapy was more effective than OHAs were in maintaining long-term glycemic control and inducing glycemic remission (HbA1c ≤ 6.5% without OHAs) after 5 years.[99]

When viewed from a different perspective, the role of the intensity of β-cell "rest" in their beneficial effects on β-cell function was questioned because of results observed in patients with T2D receiving prolonged insulin treatment. A rapidly induced enhancement in the glucagon-stimulated C-peptide level and a decrease in the proinsulin/insulin ratio were observed in patients with T2D after insulin treatment.[100] However, prolonged treatment with insulin did not further enhance β-cell function despite the fact that this treatment successively improved metabolic control. By contrast, extended treatment with insulin for 6 months in patients with newly diagnosed T2D significantly improved the HOMA-β index, area under the insulin curve, and insulinogenic index compared with OHA treatment only.[101] This discrepancy might be partly attributable to different patient populations; however, the duration of diabetes and the extent of β-cell rest might affect the preservation of β-cell function.

IIT has improved β-cell function and extended remission (off medication) in most of the aforementioned studies, indicating that IIT preserves β-cell function. However, the duration of IIT required to reach optimal improvement in β-cell function remains unclear. The beneficial effects of IIT on β-cell function may depend on the duration of the presence of T2D. The more efficient preservation or improvement of β-cell function observed in patients with newly diagnosed T2D than in those with long-term diabetes may be attributed to the presence of more numerous recoverable β-cells in patients with newly diagnosed T2D.

Conclusion

This article reviewed findings regarding the efficacy of currently available clinical approaches to preserve β-cell mass and function in the management of T2D. To date, no uniformly effective therapy for β-cell preservation has been developed. However, the studies reviewed herein have suggested several treatment modalities that, if delivered early in the course of T2D when β-cell dysfunction is reversible, have potential to preserve β-cell function and mass in the short and long term. The application of such interventions after the occurrence of profound β-cell failure is less likely to result in the remission of β-cell mass and function. Thus, the application of aggres-

sive therapeutic interventions resulting in the maintenance and often improvement of β-cell function and mass after T2D diagnosis can be an effective treatment option. Although considerable information regarding the significant β-cell protective effects of OHAs and IIT has been obtained because of the growing body of evidence from clinical trials, many issues remain unclear. Future research on this topic should include comparative trials of different interventions in individuals with newly diagnosed T2D that incorporate currently available medications and strategies for β-cell preservation.

References

1. Brooks-Worrell B, Palmer JP: Is diabetes mellitus a continuous spectrum? Clin Chem 2011;57:158-61. doi: 10.1373/clinchem.2010.148270.
2. Butler AE, Janson J, Bonner-Weir S, et al: β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-10. doi: 10.2337/diabetes.52.1.102.
3. Schofield CJ, Sutherland C: Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. Diabet Med 2012;29:972-9. doi: 10.1111/j.1464-5491.2012.03655.x.
4. Rahier J, Guiot Y, Goebbels RM, et al: Pancreatic β-cell mass in European subjects with type 2 diabetes. Diabetes Obes Metab 2008;10:32-42. doi: 10.1111/j.1463-1326.2008.00969.x.
5. Kendall DM, Cuddihy RM, Bergenstal RM: Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. Eur J Intern Med 2009;20:S329-39. doi: 10.1016/j.ejim.2009.05.009.
6. Hanley S: Pancreatic β-cell mass as a pharmacologic target in diabetes. Mcgill J Med 2009;12:51. doi: 10.26443/mjm.v12i2.267.
7. Kahn SE, Prigeon RL, McCulloch DK, et al: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42:1663-72. doi: 10.2337/diab.42.11.1663.
8. Westermark P, Wilander E: The influence of amyloid deposits on the islet volume in maturity onset diabetes mellitus. Diabetologia 1978;15:417-21. doi: 10.1007/BF01219652.
9. Sakuraba H, Mizukami H, Yagihashi N, et al: Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. Diabetologia 2002;45:85-96. doi: 10.1007/s125-002-8248-z.
10. Yoon KH, Ko SH, Cho JH, et al: Selective β-cell loss and α-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 2003;88:2300-8. doi: 10.1210/jc.2002-020735.
11. Chen C, Cohrs CM, Stertmann J, et al: Human beta cell mass and function in diabetes: recent advances in knowledge and technologies to understand disease pathogenesis. Mol Metab 2017;6:943-57. doi: 10.1016/j.molmet.2017.06.019.
12. Halban PA, Polonsky KS, Bowden DW, et al: β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. J Clin Endocrinol Metab 2014;99:1983-92. doi: 10.1210/jc.2014-1425.
13. Giaccari A, Sorice G, Muscogiuri G: Glucose toxicity: the leading actor in the pathogenesis and clinical history of type 2 diabetes–mechanisms and potentials for treatment. Nutr Metab Cardiovasc Dis 2009;19:365-77. doi: 10.1016/j.numecd.2009.03.018.
14. Weir GC, Marselli L, Marchetti P, et al: Towards better understanding of the contributions of overwork and glucotoxicity to the β-cell inadequacy of type 2 diabetes. Diabetes Obes Metab 2009;11 Suppl:82-90. doi: 10.1111/j.1463-1326.2009.01113.x.
15. Lytrivi M, Castell A L, Poitout V, et al: Recent insights into mechanisms of β-cell lipo-and glucolipotoxicity in type 2 diabetes. J Mol Biol 2020;432:1514-34. doi: 10.1016/j.jmb.2019.09.016.
16. Maedler K, Sergeev P, Ris F, et al: Glucose-induced β cell production of IL-1β contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002;110:851-60. doi: 10.1172/JCI200215318.
17. Maedler K, Sergeev P, Ehses JA, et al: Leptin modulates β cell expression of IL-1 receptor antagonist and release of IL-1β in human islets. Proc Natl Acad Sci 2004;101:8138-43. doi: 10.1073/pnas.0305683101.
18. Gupta D, Leahy JL: Islet amyloid and type 2 diabetes: overproduction or inadequate clearance and detoxification? J Clin Invest 2014;124:3292-4. doi: 10.1172/JCI77506.
19. Slentz CA, Tanner CJ, Bateman LA, et al: Effects of exercise training intensity on pancreatic β-cell function. Diabetes Care 2009;32:1807-11. doi: 10.2337/dc09-0032.
20. Kelley DE, Wing R, Buonocore C, et al: Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1993;77:1287-93. doi: 10.1210/jcem.77.5.8077323.
21. Malin SK, Solomon TP, Blaszczak A, et al: Pancreatic β-cell function increases in a linear dose-response manner following exercise training in adults with prediabetes. Am J Physiol Endocrinol Metab 2013;305:E1248-54. doi: 10.1152/ajpendo.00260.2013.
22. Solomon TP, Haus JM, Kelly KR, et al: Improved

pancreatic β-cell function in type 2 diabetic patients after lifestyle-induced weight loss is related to glucose-dependent insulinotropic polypeptide. Diabetes care 2010;33:1561-6. doi: 10.2337/dc09-2021.
23. Marchetti P, Del Guerra S, Marselli L, et al: Pancreatic islets from type 2 diabetic patients have functional defects and increased apoptosis that are ameliorated by metformin. J Clin Endocr Metab 2004;89:5535-41. doi: 10.1210/jc.2004-0150.
24. Hashemitabar M, Bahramzadeh S, Saremy S, et al: Glucose plus metformin compared with glucose alone on β cell function in mouse pancreatic islets. Biomed Rep 2015;3:721-5. doi: 10.3892/br.2015.476.
25. Lablanche S, Cottet-Rousselle C, Lamarche F, et al: Protection of pancreatic INS-1 β-cells from glucose-and fructose-induced cell death by inhibiting mitochondrial permeability transition with cyclosporin A or metformin. Cell Death Dis 2011;2:e134. doi: 10.1038/cddis.2011.15.
26. Simon-Szabó L, Kokas M, Mandl J, et al: Metformin attenuates palmitate-induced endoplasmic reticulum stress, serine phosphorylation of IRS-1 and apoptosis in rat insulinoma cells. PLoS One 2014;9:e97868. doi: 10.1371/journal.pone.0097868.
27. Kitabchi AE, Temprosa M, Knowler WC, et al: Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. Diabetes 2005;54:2404-14. doi: 10.2337/diabetes.54.8.2404.
28. RISE Consortium: Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care 2018;41:1717-25. doi: 10.2337/dc18-0787.
29. Tajima A, Hirata T, Taniguchi K, et al: Combination of TS-021 with metformin improves hyperglycemia and synergistically increases pancreatic β-cell mass in a mouse model of type 2 diabetes. Life Sci 2011;89:662-70. doi: 10.1016/j.lfs.2011.08.005.
30. Maedler K, Carr RD, Bosco D, et al: Sulfonylurea induced β-cell apoptosis in cultured human islets. J Clin Endocrinol Metab 2005;90:501-6. doi: 10.1210/jc.2004-0699.
31. U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes 1995;44:1249-58 doi: 10.2337/diabetes.44.11.1249. Erratum in: Diabetes 1996 Nov;45:1655.
32. Del Guerra S, Marselli L, Lupi R, et al: Effects of prolonged in vitro exposure to sulphonylureas on the function and survival of human islets. J Diabetes Complication 2005;19:60-4. doi: 10.1016/j.jdiacomp.2004.05.001.
33. Takahashi A, Nagashima K, Hamasaki A, et al: Sulfonylurea and glinide reduce insulin content, functional expression of K(ATP) channels, and accelerate apoptotic β-cell death in the chronic phase. Diabetes Res Clin Pract 2007;77:343-50. doi: 10.1016/j.diabres.2006.12.021.
34. Kimoto K, Suzuki K, Kizaki T, et al: Gliclazide protects pancreatic β-cells from damage by hydrogen peroxide. Biochem Biophys Res Commun 2003;303:112-9. doi: 10.1016/S0006-291X(03)00310-3.
35. Karam JH, Sanz N, Salamon E, et al: Selective unresponsiveness of pancreatic β-cells to acute sulfonylurea stimulation during sulfonylurea therapy in NIDDM. Diabetes 1986;35:1314-20. doi: 10.2337/diab.35.12.1314. Erratum in: Diabetes 1987;36:following 406.
36. Hotta N, Kakuta H, Sano T, et al: Long-term effect of acarbose on glycaemic control in non-insulin-dependent diabetes mellitus: a placebo-controlled double-blind study. Diabet Med 1993;10:134-8. doi: 10.1111/j.1464-5491.1993.tb00030.x.
37. Meneilly GS, Ryan EA, Radziuk J, et al: Effect of acarbose on insulin sensitivity in elderly patients with diabetes. Diabetes Care 2000;23:1162-7. doi: 10.2337/diacare.23.8.1162.
38. Chang AM, Smith MJ, Bloem CJ, et al: Effect of lowering postprandial hyperglycemia on insulin secretion in older people with impaired glucose tolerance. Am J Physiol Endocrinol Metab 2004;287:E906-11. doi: 10.1152/ajpendo.00156.2004.
39. Hanefeld M, Fischer S, Schulze J, et al: Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. Diabetes Care 1991;14:732-7. doi: 10.2337/diacare.14.8.732.
40. Rossetti L, Giaccari A, De Fronzo RA: Glucose toxicity. Diabetes Care 1990;13:610-30. doi: 10.2337/diacare.13.6.610.
41. Reaven GM, Lardinois CK, Greenfield MS, et al: Effect of acarbose on carbohydrate and lipid metabolism in NIDDM patients poorly controlled by sulfonylureas. Diabetes Care 1990;13 Suppl 3:32-6. doi: 10.2337/diacare.13.3.32.
42. Schnack D, Prager RJF, Winkler J, et al: Effects of 8-week alpha-glucosidase inhibitor on metabolic control, C-peptide secretion, hepatic glucose output, and peripheral insulin sensitivity in poorly controlled type 2 diabetic patients. Diabetes Care 1989;12:537-43. doi: 10.2337/diacare.12.8.537.
43. Seifarth C, Bergmann J, Holst JJ, et al: Prolonged and enhanced secretion of glucagon-like peptide 1 (7–36 amide) after oral sucrose due to alpha glucosidase inhibition (acarbose) in Type 2 diabetic patients. Diabet Med 1998;15:485-91. doi: 10.1002/(SICI)1096-9136(199806)15:6<485::AID-DIA610>3.0.CO;2-Y.
44. Akiyama M, Hatanaka M, Ohta Y, et al: Increased insulin demand promotes while pioglitazone prevents pancreatic beta cell apoptosis in Wfs1 knockout mice. Diabetologia 2009;52:653-63. doi: 10.1007/s00125-009-1270-6.
45. Lupi R, Del Guerra S, Marselli L, et al:

Rosiglitazone prevents the impairment of human islet function induced by fatty acids: evidence for a role of PPARgamma2 in the modulation of insulin secretion. Am J Physiol Endocrinol Metab 2004;286:E560-7. doi: 10.1152/ajpendo.00561.2002.
46. Szalkowski D, White-Carrington S, Berger J, et al: Antidiabetic thiazolidinediones block the inhibitory effect of tumor necrosis factor-α on differentiation, insulin-stimulated glucose uptake, and gene expression in 3T3-L1 cells. Endocrinology 1995;136:1474-81. doi: 10.1210/endo.136.4.7895657.
47. Cavaghan MK, Ehrmann DA, Byrne MM, et al: Treatment with the oral antidiabetic agent troglitazone improves β cell responses to glucose in subjects with impaired glucose tolerance. J Clin Invest 1997;100:530-7. doi: 10.1172/JCI119562.
48. Gastaldelli A, Ferrannini E, Miyazaki Y, et al: Thiazolidinediones improve beta-cell function in type 2 diabetic patients. Am J Physiol Endocrinol Metab 2007; 292: E871-83. doi: 10.1152/ajpendo.00551.2006.
49. DeFronzo RA, Tripathy D, Schwenke DC, et al: Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. Diabetes 2013;62:3920-6. doi: 10.2337/db13-0265.
50. DeFronzo RA, Banting Lecture: from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773-95. doi: 10.2337/db09-9028.
51. Finegood DT, McArthur MD, Kojwang D, et al: β-Cell mass dynamics in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net cell death. Diabetes 2001;50:1021-9. doi: 10.2337/diabetes.50.5.1021.
52. Ovalle F, Bell DS: Effect of rosiglitazone versus insulin on the pancreatic beta-cell function of subjects with type 2 diabetes. Diabetes Care 2004;27:2585-9. doi: 10.2337/diacare.27.11.2585.
53. Xiang AH, Peters RK, Kjos SL, et al: Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 2006;55:517-22. doi: 10.2337/diabetes.55.02.06.db05-1066.
54. Kwon MJ, Lee YJ, Jung HS, et al: The direct effect of lobeglitazone, a new thiazolidinedione, on pancreatic beta cells: a comparison with other thiazolidinediones. Diabetes Res Clin Pract 2019;151:209-23. doi: 10.1016/j.diabres.2019.04.006.
55. Matsui J, Terauchi Y, Kubota N, et al: Pioglitazone reduces islet triglyceride content and restores impaired glucose-stimulated insulin secretion in heterozygous peroxisome proliferator-activated receptor gamma-deficient mice on a high-fat diet. Diabetes 2004;53:2844-54. doi: 10.2337/diabetes.53.11.2844.
56. Rosen ED, Kulkarni RN, Sarraf P, et al: Targeted elimination of peroxisome proliferator-activated receptor gamma in beta cells leads to abnormalities in islet mass without compromising glucose homeostasis. Mol Cell Biol 2003;23:7222-9. doi: 10.1128/MCB.23.20.7222-7229.2003.
57. Gupta D, Kono T, Evans-Molina C: The role of peroxisome proliferator-activated receptor gamma in pancreatic beta cell function and survival: therapeutic implications for the treatment of type 2 diabetes mellitus. Diabetes Obes Metab 2010;12:1036-47. doi: 10.1111/j.1463-1326.2010.01299.x.
58. Pospisilik JA, Martin J, Doty T, et al: Dipeptidyl peptidase IV inhibitor treatment stimulates β-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 2003;52:741-50. doi: 10.2337/diabetes.52.3.741.
59. Shimizu S, Hosooka T, Matsuda T, et al: DPP4 inhibitor vildagliptin preserves β-cell mass through amelioration of endoplasmic reticulum stress in C/EBPB transgenic mice. J Mol Endocrinol 2012;49:125-35. doi: 10.1530/JME-12-0039.
60. Campbell JE, Drucker DJ: Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013;17:819-37. doi: 10.1016/j.cmet.2013.04.008.
61. Drucker DJ, Nauck MA: The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705. doi: 10.1016/S0140-6736(06)69705-5.
62. Omar BA, Vikman J, Winzell MS, et al: Enhanced beta cell function and anti-inflammatory effect after chronic treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin in an advanced-aged diet-induced obesity mouse model. Diabetologia 2013;56:1752-60. doi: 10.1007/s00125-013-2927-8.
63. Satoh-Asahara N, Sasaki Y, Wada H, et al: A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 2013;62:347-51. doi: 10.1016/j.metabol.2012.09.004.
64. Donath MY, Schumann DM, Faulenbach M, et al: Islet inflammation in type 2 diabetes: from metabolic stress to therapy. Diabetes Care 2008;31 Suppl 2: S161-4. doi: 10.2337/dc08-s243.
65. Ma D, Yu Y, Yu X, et al: The changes of leukocyte telomere length and telomerase activity after sitagliptin intervention in newly diagnosed type 2 diabetes. Diabetes Metab Res Rev 2015;31:256-61. doi: 10.1002/dmrr.2578.
66. Shah P, Ardestani A, Dharmadhikari G, et al: The DPP-4 inhibitor linagliptin restores β-cell function and survival in human isolated islets through GLP-1 stabilization. J Clin Endocrinol Metab 2013;98:E1163-72. doi: 10.1210/jc.2013-1029.
67. Utzschneider KM, Tong J, Montgomery B, et al: The dipeptidyl peptidase-4 inhibitor vildagliptin improves β-cell function and insulin sensitivity in subjects with impaired fasting glucose. Diabetes Care 2008;31:108-13. doi: 10.2337/dc07-1441.

68. D'Alessio DA, Denney AM, Hermiller LM, at al: Treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin improves fasting islet-cell function in subjects with type 2 diabetes. J Clin Endocrinol Metab 2009;94:81-8. doi: 10.1210/jc.2008-1135.
69. Scherbaum WA, Schweizer A, Mari A, et al: Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia. Diabetes Obes Metab 2008;10:675-82. doi: 10.1111/j.1463-1326.2008.00850.x.
70. Lyu X, Zhu X, Zhao B, et al: Effects of dipeptidyl peptidase-4 inhibitors on beta-cell function and insulin resistance in type 2 diabetes: meta-analysis of randomized controlled trials. Sci Rep 2017;7:44865. doi: 10.1038/srep44865.
71. van Genugten RE, van Raalte DH, Diamant M: Dipeptidyl peptidase-4 inhibitors and preservation of pancreatic islet-cell function: a critical appraisal of the evidence. Diabetes Obes Metab 2012;14:101-11. doi: 10.1111/j.1463-1326.2011.01473.x.
72. Esposito K, Chiodini P, Maiorino MI, et al: Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials. BMJ Open 2014;4:e005442. doi: 10.1136/bmjopen-2014-005442.
73. Leibowitz G, Cahn A, Bhatt DL, et al: Impact of treatment with saxagliptin on glycaemic stability and β-cell function in the SAVOR-TIMI 53 study. Diabetes Obes Metab 2015;17:487-94. doi: 10.1111/dom.12445.
74. Paldánius PM, Del Prato S, Stumvoll M, et al: Effect on beta cell function in newly diagnosed type 2 diabetes patients after treatment with vildagliptin and metformin: results from the VERIFY study. (Poster). In 56th EASD Annual Meeting of the European Association for the Study of Diabetes: 21-25 September 2020. Diabetologia 2020;63 Suppl 1:293.
75. Lee YS, Jun HS: Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. Metabolism 2014;63:9-19. doi: 10.1016/j.metabol.2013.09.010.
76. Garber AJ: Incretin effects on β-cell function, replication, and mass: the human perspective. Diabetes Care 2011;34: S258-63. doi: 10.2337/dc11-s230.
77. DeFronzo RA, Triplitt C, Qu Y, et al: Effects of exenatide plus rosiglitazone on β-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. Diabetes Care 2010;33:951-7. doi: 10.2337/dc09-1521.
78. Derosa G, Maffioli P, Salvadeo SA, et al: Exenatide versus glibenclamide in patients with diabetes. Diabetes Technol Ther 2010;12:233-40. doi: 10.1089/dia.2009.0141.
79. Vilsbøll T, Brock B, Perrild H, et al: Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with type 2 diabetes mellitus. Diabet Med 2008;25:152-6. doi: 10.1111/j.1464-5491.2007.02333.x.
80. Madsbad S: Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics)--reclinical and clinical results. Best Pract Res Clin Endocrinol Metab 2009; 23: 463-77. doi: 10.1016/j.beem.2009.03.008.
81. Anholm C, Kumarathurai P, Jürs A, et al: Liraglutide improves the beta-cell function without increasing insulin secretion during a mixed meal in patients, who exhibit well-controlled type 2 diabetes and coronary artery disease. Diabetol Metab Syndr 2019;11:42. doi: 10.1186/s13098-019-0438-6.
82. Okauchi S, Shimoda M, Obata A, et al: Protective effects of SGLT2 inhibitor luseogliflozin on pancreatic beta-cells in obese type 2 diabetic db/db mice. Biochem Biophys Res Commun 2016;470:772-82. doi: 10.1016/j.bbrc.2015.10.109.
83. Kimura T, Obata A, Shimoda M, et al: Protective effects of the SGLT2 inhibitor luseogliflozin on pancreatic β-cells in db/db mice: The earlier and longer, the better. Diabetes Obes Metab 2018;20:2442-57. doi: 10.1111/dom.13400.
84. Shimo N, Matsuoka TA, Miyatsuka T, et al: Short-term selective alleviation of glucotoxicity and lipotoxicity ameliorates the suppressed expression of key β-cell factors under diabetic conditions. Biochem Biophys Res Commun 2015;467:948-54. doi: 10.1016/j.bbrc.2015.10.038.
85. Daems C, Welsch S, Boughaleb H, et al: Early treatment with empagliflozin and gaba improves ß-cell mass and glucose tolerance in streptozotocin-treated mice. J Diabetes Res 2019;2019:1-14. doi: 10.1155/2019/2813489.
86. Macdonald FR, Peel JE, Jones HB, et al: The novel sodium glucose transporter 2 inhibitor dapagliflozin sustains pancreatic function and preserves islet morphology in obese, diabetic rats. Diabetes Obes Metab 2010;12:1004-12. doi: 10.1111/j.1463-1326.2010.01291.x.
87. Tanday N, Irwin N, Flatt PR, et al: Dapagliflozin exerts positive effects on beta cells, decreases glucagon and does not alter beta-to alpha-cell transdifferentiation in mouse models of diabetes and insulin resistance. Biochem Pharmacol 2020; 177:114009. doi: 10.1016/j.bcp.2020.114009.
88. Merovci A, Mari A, Solis-Herrera C, et al: Dapagliflozin lowers plasma glucose concentration and improves β-cell function. J Clin Endocrinol Metab 2015;100:1927-32. doi: 10.1210/jc.2014-3472.
89. Al Jobori H, Daniele G, Adams J, et al: Empagliflozin treatment is associated with improved β-cell function in type 2 diabetes mellitus. J Clin Endocrinol Metab 2018;103:1402-7. doi: 10.1210/jc.2017-01838.
90. Takahara M, Shiraiwa T, Matsuoka TA, et al: Ameliorated pancreatic β cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. Endocrine J

2015;62:77-86. doi: 10.1507/endocrj.EJ14-0335.
91. Rosenstock J, Aggarwal N, Polidori D, et al: Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232-8. doi: 10.2337/dc11-1926.
92. Bonner C, Kerr-Conte J, Gmyr V, et al: Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512-7. doi: 10.1038/nm.3828.
93. Aspinwall CA, Lakey JR, Kennedy RT: Insulin-stimulated insulin secretion in single pancreatic beta cells. J Biol Chem 1999;274:6360-5. doi: 10.1074/jbc.274.10.6360.
94. Garvey WT, Olefsky JM, Griffin J, et al: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985;34: 222-34. doi: 10.2337/diabetes.34.3.222.
95. Wang D, Sun L, Song G, et al: Effects of intensive insulin therapy upon pancreatic β cell function in patients newly diagnosed with type II diabetes. Int J Clin Exp Med 2015;8:1391-5.
96. Weng J, Li Y, Xu W, et al: Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371:1753-60. doi: 10.1016/S0140-6736(08)60762-X.
97. Li Y, Xu W, Liao Z, et al: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. Diabetes Care 2004;27:2597-602. doi: 10.2337/diacare.27.11.2597.
98. Ryan EA, Imes S, Wallace C: Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 2004;27:1028-32. doi: 10.2337/diacare.27.5.1028.
99. Chen HS, Wu TE, Kuo CS: Long-term glycemic control after 6 months of basal insulin therapy. Am J Manag Care 2014; 20: e369-79.
100. Kärvestedt L, Andersson G, Efendic S, et al: A rapid increase in beta-cell function by multiple insulin injections in type 2 diabetic patients is not further enhanced by prolonging treatment. J Intern Med 2002;251:307-16. doi: 10.1046/j.1365-2796.2002.00956.x.
101. Chen HS, Wu TE, Jap TS, et al: Beneficial effects of insulin on glycemic control and beta cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. Diabetes Care 2008;31:1927-32. doi: 10.2337/dc08-0075.