

Interventions to Preserve Beta-Cell Function in the Management and Prevention of Type 2 Diabetes

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Abstract

The International Diabetes Federation estimates that there are currently 336 million people worldwide who have type 2 diabetes (T2DM), and the global prevalence of diabetes has more than doubled since 1980. The rapid rise in rates of T2DM echoes a similar rise in rates of obesity, which causes insulin resistance and places an increased insulin secretory demand on pancreatic β cells. While diabetes is diagnosed clinically by elevated plasma glucose levels, loss of β -cell function is progressive over time and β -cell dysfunction is far advanced by the time diabetes is diagnosed. Methods for preserving or restoring β -cell function are important for the prevention and treatment of T2DM. Interventions that reduce body fat or that change fat biology provide the best evidence for slowing or arresting the deterioration of β -cell function that causes T2DM. These interventions should form the basis of interventions to prevent and treat T2DM, particularly early in its course.

Keywords

Diabetes; Prevention; β -cell function; Glucose; Type 2 diabetes

Introduction

The global prevalence of diabetes mellitus has more than doubled since 1980 and is expected to continue to rise at alarming rates [1]. An estimated 336 million people worldwide now have T2DM [2]. T2DM results from an interaction between genetic and environmental factors that impair β -cell function and insulin action. Diabetes is diagnosed clinically by elevated plasma glucose levels, however, loss of β -cell function is progressive over time and β -cell dysfunction is far advanced by the time diabetes is diagnosed clinically [3, 4]. Patients with impaired glucose tolerance have <50 % of normal β -cell function [5–7] and patients with T2DM have <15 % of normal β -cell function for their degree of insulin resistance [8], demonstrating the progressive nature of β -cell dysfunction in the course of T2DM. Therefore, methods for preserving or restoring β -cell function are important in our

attempts to prevent and treat T2DM. In this review, we discuss current evidence for causes of the progressive loss of β -cell function in T2DM, and the effects of current therapeutic strategies on preservation of β -cell function and the prevention and treatment of T2DM.

Pathogenesis of Type 2 Diabetes

β -cell Compensation for Insulin Resistance

Diabetes is defined clinically as an increase in plasma glucose levels. Plasma glucose levels are determined by the sensitivity of tissues to insulin and by the amount of insulin secreted by the pancreatic β cells. A number of factors, including lack of exercise, obesity, and visceral fat are major determinants of insulin resistance [4].

Normally, increases in insulin resistance are matched by a compensatory increase in insulin secretion by the β cells, and the relationship between insulin resistance and insulin secretion is defined by a hyperbola [9]. Based on this hyperbolic relationship, β -cell compensation can be determined by the disposition index, defined as the product of insulin secretion and insulin sensitivity [9] (Fig. 1). As long as the product of insulin secretion times insulin sensitivity remains constant, glucose tolerance is preserved. For example, in a lean, insulin sensitive individual, less insulin secretion is required to maintain normal glucose levels. An obese, insulin resistant individual requires a compensatory increase in insulin secretion in order to maintain normal glucose levels. Inadequate β -cell compensation for insulin resistance results in impaired glucose homeostasis and eventually to T2DM. Longitudinal studies have shown that reduced β -cell function as reflected in the disposition index is a powerful predictor of conversion from normal glucose tolerance to T2DM in at-risk populations [10, 11].

Multiple factors, including genetic predisposition, glucotoxicity, lipotoxicity, and decreased β -cell mass and function are thought to play a role in the pathogenesis of T2DM [2, 4].

Glucotoxicity and Lipotoxicity

Glucotoxicity refers to irreversible damage to pancreatic β cells caused by chronically elevated glucose levels and has been demonstrated with in vitro and in vivo studies [12–14]. Similarly to chronically elevated glucose levels, chronically elevated levels of free fatty acids (FFA) are known to cause β -cell dysfunction, a concept referred to as lipotoxicity [12]. Obesity, especially abdominal adiposity, results in increased FFA levels, and has been shown to correlate with decreased insulin gene expression and β -cell death [12]. In vitro and in vivo studies using lipid infusions have shown that chronic exposure to FFA results in decreased glucose stimulated insulin secretion, decreased insulin gene expression, and increased β -cell apoptosis in β cell lines and isolated human islets [15–17]. Recently, the concept of “glucolipotoxicity” has been introduced because of evidence suggesting that lipotoxicity is dependent on the simultaneous presence of hyperglycemia, and that elevated glucose and FFA act synergistically to impair β -cell function [12, 15, 18].

Two proposed mechanisms for glucotoxicity are endoplasmic reticulum (ER) stress and oxidative stress [15, 19].

ER Stress

The ER is the organelle responsible for folding, modification, and trafficking of proteins [20]. β cells are particularly rich in ER, given their secretory function. ER stress occurs when the ER's folding capacity cannot match the protein load, and unfolded or misfolded proteins accumulate in the ER's lumen [12]. Chronic hyperglycemia increases the production demand on β cells, which puts them at risk for ER stress. As the β cells of

hyperglycemic individuals increase their preproinsulin production to account for elevated glucose levels, misfolded proinsulin may result in ER stress [12].

It is important to note that the processing of proinsulin into mature insulin is a critical step in insulin production and secretion, and high proinsulin levels relative to circulating levels of mature insulin can indicate β -cell stress. Recent genome-wide association studies (GWAS) have identified 9 genetic variants associated with fasting proinsulin that may contribute to β -cell function and susceptibility for T2DM [21].

When ER stress occurs, a number of different stress responses collectively referred to as the unfolded protein response (UPR) are activated in an attempt to restore cell function [20]. This is accomplished by (a) decreased translation, (b) increased ER folding capacity, (c) ER stress associated protein degradation and, ultimately (d) cell apoptosis if a, b, and c are unsuccessful [12].

ER stress also results in increased production of molecular chaperones, which help with protein folding, such as 78 kDa glucose-regulated protein (GRP78) and 4-phenylbutyrate (PBA) [19]. A recent study reported that glucose infusion to rats for 48 hours increased ER stress markers and induced β -cell dysfunction, but co-infusion with the chaperone molecule PBA prevented glucose-induced β -cell dysfunction [19].

Oxidative Stress

In vitro and in vivo studies implicate oxidative stress in glucose-induced β -cell dysfunction [19, 22, 23]. As glucose is metabolized in the mitochondria via oxidative phosphorylation, reactive oxygen species (ROS) are produced. As studies involving rat islets have shown, ROS reduce the ability of the mitochondria to produce ATP, thereby decreasing glucose-stimulated insulin secretion [24]. Isolated islets from T2DM patients have increased markers of oxidative stress compared with islets from controls without T2DM, and levels of oxidative stress correlate with the degree of impairment in glucose-stimulated insulin secretion [23]. Moreover, exposure to the antioxidant, glutathione, for 24 hours was shown to significantly improve glucose-stimulated insulin release and resulted in decreased markers of oxidative stress suggesting that reducing islet cell oxidative stress may improve the functional impairment of T2DM islets [23].

Reduced β -Cell Mass

A number of studies have demonstrated that β -cell mass and/or volume is reduced in patients with T2DM [25–29]. In a study examining pancreatic tissue from 124 autopsies, relative β -cell volume was found to be increased by 50 % in obese individuals without T2DM when compared with lean individuals without T2DM. In contrast, in obese individuals with impaired fasting glucose (IFG) there was a 40 % deficit in β -cell volume and in obese individuals with T2DM there was a 63 % deficit in β -cell volume when compared with obese individuals without T2DM [27]. The presence of decreased β -cell volume in individuals with IFG suggests that this process occurs early on in the process of developing T2DM [27].

Effects of Type 2 Diabetes Therapies on β -Cell Function

Clinical management of T2DM is currently based on achieving plasma glucose levels that are associated with a low risk of developing long-term microvascular complications [30]. There are a number of therapies that are effective in reducing plasma glucose levels through various mechanisms, however current therapeutic strategies have different effects on β -cell function. Interventions that reduce the load on β -cells by decreasing insulin demand have better durability on glycemic control and are more effective in preventing T2DM in high

risk patients. Below, we discuss current therapies used in the treatment of T2DM and their effects on β -cell function, long-term durability, and effectiveness in preventing progression to T2DM in high risk individuals.

Intensive Lifestyle Modification

Obesity is a major risk factor for T2DM, and the increased prevalence of obesity is largely responsible for the concomitant increase in T2DM [1]. Obesity and lack of physical activity cause insulin resistance and increase the workload on β cells [31]. Weight loss and exercise interventions increase insulin sensitivity and unload the secretory demand on β -cells.

The United States Diabetes Prevention Program (DPP) showed that implementing a program that achieved at least a 7 % reduction in body weight through diet and exercise reduced the incidence of T2DM by 58 % in patients with impaired glucose tolerance (IGT) [32]. The effect of lifestyle intervention on reducing the incidence of T2DM was related to overall improvements in β -cell function driven by its gains in insulin sensitivity, such that the hyperbola describing the relationship between insulin secretion and insulin sensitivity was shifted to the right [33]. The Finnish Diabetes Prevention Study (DPS) also showed a 58 % reduction in the incidence of T2DM in individuals with IGT who were assigned to a lifestyle intervention that included weight loss and increased physical activity [34] (Table 1). A recent analysis of the DPS indicated that lifestyle intervention helps to preserve β -cell function and prevent the development of T2DM through improvements in insulin sensitivity [35].

Pharmacological Weight Loss

The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study reported that orlistat, a gastrointestinal lipase inhibitor, added to lifestyle intervention resulted in greater weight loss and a 37 % reduced relative risk for diabetes compared with lifestyle intervention alone in obese adults with normal and impaired glucose tolerance [36]. In obese subjects with IGT at baseline, orlistat plus lifestyle intervention resulted in a 45 % reduced relative risk for diabetes vs lifestyle intervention alone (Table 1).

These randomized controlled trials demonstrate the importance of lifestyle modifications and pharmacological weight loss in T2DM prevention, but it is important to note that weight regain is common [37], even with pharmacological treatment. For example, in the XENDOS trial, mean weight loss after the first year of treatment was 10.6 kg with orlistat plus lifestyle intervention and 6.2 kg after lifestyle intervention alone, but after 4 years of treatment the mean weight loss was only 5.8 kg in orlistat plus lifestyle and 3.0 kg in lifestyle intervention alone [36]. Therefore, early intervention measures, including public health initiatives aimed at preventing obesity by promoting physical activity and healthier diets early in life may be particularly important to prevent the upward trends in prevalence of T2DM. For obese individuals with impaired glucose levels, interventions aimed at more robust and sustained weight loss, including modestly invasive bariatric surgery, deserve exploration as an approach towards β -cell preservation for the prevention of T2DM [38] (see “On the Horizon; Newer Approaches” below).

Sulfonylureas

Sulfonylureas are oral medications that stimulate insulin secretion by binding to the sulfonylurea receptor 1, resulting in membrane depolarization and calcium influx, which triggers exocytosis of insulin containing secretory granules [39]. While sulfonylureas are widely used clinically in the treatment of T2DM, evidence from the Diabetes Outcome Progression Trial (ADOPT) study demonstrates a more rapid deterioration of glycemic control with the sulfonylurea, glyburide, compared with treatment with metformin and the

thiazolidinedione (TZD), rosiglitazone in patients with recently diagnosed T2DM [40]. In vitro studies have suggested that the lack of durability of sulfonylurea treatment observed in clinical studies may be due to its potentially damaging effects on pancreatic β -cells [41, 42]. Studies in isolated human islets indicate that the sulfonylurea, glibenclamide, decreases insulin content, and induces β -cell apoptosis [41, 42]; however, 1 study suggested that the sulfonylurea, gliclazide, may protect β cells from apoptosis potentially through antioxidant effects [42]. No clinical studies have demonstrated a beneficial effect of sulfonylureas in the prevention of T2DM, and as mentioned above, sulfonylurea monotherapy has less durable effects on glycemic control compared with a TZD or metformin in patients recently diagnosed with T2DM [40].

Metformin

Metformin is effective at reducing hyperglycemia primarily by inhibiting hepatic glucose production and by increasing insulin sensitivity [43]. It is currently recommended as a first-line drug for the treatment of T2DM [30]. In vitro studies demonstrated that metformin could protect isolated human islets from glucotoxicity and lipotoxicity suggesting that metformin may have beneficial effects on β -cell health [44, 45]. In clinical studies, the DPP showed that metformin reduced the conversion from IGT to T2DM by 31 % [32] suggesting that it has modest effects on slowing the progression of T2DM (Table 1). The U.K. Prospective Diabetes Study (UKPDS) showed similar rates of deterioration of β -cell function (assessed with HOMA-B index) and loss of glycemic control with metformin treatment compared with sulfonylureas or insulin treatment in patients with recently diagnosed T2DM [46, 47]. The ADOPT study showed that the durability of metformin monotherapy was better than glyburide, but it still resulted in a 21 % failure rate at 5 years in patients with recently diagnosed T2DM [40].

Acarbose

Acarbose is an α -glucosidase inhibitor that improves post-prandial hyperglycemia by inhibiting the activity of enzymes in the small intestine resulting in reduced glucose absorption. The Study to Prevent NIDDM (STOP-NIDDM) found a 25 % relative risk reduction in the development of T2DM over 3.3 years in patients with impaired glucose levels treated with acarbose compared with placebo [48] (Table 1). However, in the 3-month observation period after acarbose was discontinued, the incidence of diabetes in patients who had not converted was higher in the group initially assigned to acarbose (15 %) compared with group first randomized to placebo (10 %) suggesting that the benefit of acarbose is lost after discontinuation of active treatment [48].

Thiazolidinediones (TZDs)

TZDs are potent insulin sensitizers that improve glycemic control in patients with T2DM [43, 49]. TZDs are ligands for the nuclear transcription factor peroxisome-proliferator-activated-receptor- γ , and they have a wide spectrum of action [49]. Studies have shown that TZDs reduce lipotoxicity [50, 51], prevent β -cell apoptosis [52], increase serum adiponectin levels [53], and improve β -cell function [54–57]. Prevention trials have consistently shown that TZDs are effective in preventing the onset of type 2 diabetes in high-risk patients by ~50 %–75 % (DPP, Troglitazone in Prevention of Diabetes (TRIPOD), Pioglitazone in Prevention of Diabetes (PIPOD), Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM), and Actos now (ACT-NOW) [55, 56, 58–60] (see Table 1). The TRIPOD study was the first to carefully examine changes in β -cell function through treatment of insulin resistance as a way to reduce T2DM risk. Notably, the TRIPOD study showed that protection from diabetes in women with previous gestational diabetes persisted 8 months after T2DM treatment stopped, and patients who were protected from diabetes during TZD treatment had stable β -cell function and insulin resistance for almost 5

years demonstrating that TZDs slow the natural progression of the disease [55, 56]. The ability of TZDs to slow or stop progression to T2DM was supported by DREAM and DPP, in which the protection from diabetes that was achieved during treatment persisted after treatment was stopped [61].

The ADOPT Study demonstrated that TZDs had significantly greater durability for glycemic control in patients with recently diagnosed T2DM when compared with both metformin and sulfonylureas [40]. Subsequent analysis of the ADOPT data showed that the reduction in treatment failure with rosiglitazone corresponded with improved β -cell function and increased insulin sensitivity [62] supporting results from the TRIPOD prevention study and suggesting that TZDs may preserve β -cell function by improving insulin sensitivity and unloading the secretory demand on β -cells [55].

The clinical use of TZDs for the prevention of T2DM is limited due to adverse side effects, including fluid retention and weight gain, and recent safety concerns including reports of an association with increased risk for bone fractures and bladder cancer [49]. The development of safer compounds with selective PPAR γ modulation offers the potential for targeted insulin sensitization in the absence of adverse side effects [49].

GLP-1 Receptor Agonists

Glucagon-like polypeptide-1 (GLP-1) is an incretin hormone secreted by the L cells in the intestines in response to nutrient stimulation. GLP-1 possesses a number of properties that make it an ideal agent for the treatment of T2DM. GLP-1 potentiates glucose stimulated insulin secretion, suppresses glucagon secretion, delays gastric emptying and suppresses appetite [43]. GLP-1 is cleaved by the enzyme dipeptidyl peptidase-4 (DPP-4) leading to its rapid inactivation, but DPP-4 resistant GLP-1 receptor agonists, including exenatide and liraglutide, and DPP-4 inhibitors have been developed for the treatment of T2DM [43]. Studies in animals have shown the GLP-1 analogues decrease β -cell apoptosis and increase β -cell mass [63–65], and human studies indicate that exenatide exerts potent anti-inflammatory effects that are independent of weight loss [66]. Findings from recent randomized controlled trials demonstrate that exenatide improves β -cell function [67, 68, 69•, 70••]. Bunck and colleagues compared the effects of exenatide with the insulin, glargine, on β -cell function over 3 years in metformin treated patients with T2DM [68, 69•]. They found that exenatide significantly improved β -cell function during 52 weeks of active treatment compared with glargine, but after stopping the treatments for 4 weeks, β -cell function returned to pre-treatment values in both groups [68]. In contrast, in the 3-year extension study, β -cell function was sustained in the exenatide group after a 4-week off-drug period whereas the glargine treated patients had a reduction in β -cell function suggesting that at least 3 years of exenatide treatment may be necessary to delineate a significant, prolonged benefit on β -cell function [69•].

A recent study in obese adults showed that a 20-week treatment with liraglutide (in doses ranging from 1.8 to 3 mg per day) resulted in greater weight loss and an 84 %–96 % reduction in the prevalence of prediabetes compared with placebo [71••]. Another clinical trial showed that a 24-week treatment with exenatide plus lifestyle modification resulted in greater weight loss and normalization of glucose tolerance in 77 % of obese participants with impaired glucose homeostasis (IGT or IFG) compared with 56 % in the placebo group [72•]. Longer term prevention trials in high-risk patients are needed to determine whether GLP-1 agonists can modify the progressive course of T2DM.

A recent randomized controlled trial suggested that the GLP-1 receptor agonist, exenatide, may have durable effects on glycemic control in patients with T2DM [70••]. The EUREXA study compared exenatide with glimepiride as add-on to metformin for durability of

glycemic control in patients with T2DM who were inadequately controlled with metformin alone [70••]. Results showed that glycemic control was maintained for longer (180 weeks with exenatide vs 142 weeks with glimepiride) and treatment failure was lower in the exenatide (41 %) compared with glimepiride (54 %) group over the 48 month follow up period. The exenatide group also had a significantly greater increase in disposition index compared with the glimepiride group demonstrating beneficial effects of exenatide on β -cell function [70••].

On the Horizon; Newer Approaches

Early Intensive Treatment with Insulin and/or Multiple Agents

In vitro studies investigating the effects of glucose toxicity on a pancreatic β -cell line showed that shortening the duration of antecedent glucose toxicity increases the likelihood of recovering β -cell function [73]. Thus, early and more aggressive treatment strategies that quickly normalize glucose levels in patients with newly diagnosed T2DM may preserve residual β -cell function by reducing glucotoxicity. Clinical studies have shown beneficial effects of early short-term (2–3 weeks) intensive insulin therapy in patients with newly diagnosed T2DM [74–78]. A multi-center randomized trial showed that early, short-term intensive insulin treatment at the time of T2DM diagnosis led to improved β -cell function and greater diabetes remission rates at 1 year compared with early, short-term treatment with oral hypoglycemic agents [75]. A recent randomized control trial evaluated β -cell function preservation after 3.5 years of intensive therapy with insulin plus metformin compared with triple oral therapy with metformin, glyburide, and pioglitazone after an initial 3-month insulin treatment period and found that both approaches were effective in preserving β -cell function [77]. Based on these results, the authors suggested that patients with newly diagnosed T2DM should be treated with an initial period of intensive insulin therapy to maximize β -cell recovery and then continued either on insulin therapy or switched to a combination of oral agents with complementary mechanisms of action [77].

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial recently reported results of the comparison between treatment with insulin glargine to normalize fasting plasma glucose levels compared with standard care on cardiovascular outcomes, cancer, and incident diabetes in over 12,000 patients with cardiovascular disease risk factors plus IFG or T2DM who were followed for a median of 6.2 years [79]. They found that glargine had a neutral effect on cardiovascular outcomes and cancers, but that it reduced new-onset diabetes among the participants without diabetes at randomization providing support for the idea that the early use of insulin may preserve β -cell function in patients with impaired glucose homeostasis.

There is a growing interest in the early use of combination therapies for the treatment of patients with IGT and T2DM [67, 80]. A recent clinical study examined the effects of combination therapy with exenatide and rosiglitazone vs each therapy alone on insulin sensitivity and β -cell function in patients with T2DM already on metformin [67]. The 20-week combination therapy with exenatide and rosiglitazone resulted in greater improvements in insulin sensitivity and β -cell function and better glycemic control compared with either treatment alone suggesting a beneficial effect of the combination therapy [67]. However, randomized controlled studies are needed to determine whether early use of a combination of oral agents is effective in preventing T2DM in high risk patients and the long-term durability of this treatment strategy on glycemic control.

Bariatric Surgery

Bariatric surgery is an effective and durable treatment for obesity and provides substantial improvements in glycemic control in obese patients with T2DM [81]. Four bariatric surgical

procedures are used conventionally, including Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), biliopancreatic diversion (BPD), and laparoscopic sleeve gastrectomy (LSG), and RYGB and LAGB are the most widely used surgical procedures [81]. A meta-analysis indicated that bariatric surgery results in resolution of diabetes in 78 % of patients with T2DM demonstrating its significant impact on T2DM remission [82]. The effects of bariatric surgery on β -cell function were recently summarized in a review by Bradley et al [83], and indicate that LAGB surgery increases the disposition index following modest weight loss, RYGB surgery increases the disposition index after significant weight loss, BPD surgery increases early insulin secretion and disposition index in patients with T2DM, and LSG surgery increases early insulin secretion in patients with T2DM, but its effects on disposition index are currently unknown [83].

Three randomized controlled trials have compared the effects of bariatric surgery to medical therapy on remission of T2DM, and all 3 studies showed that bariatric surgery was significantly more effective than medical therapy in achieving remission of T2DM within 1 to 2 years following surgery [84, 85••, 86••]. The first randomized controlled trial showed that LAGB surgery resulted in T2DM remission in 73 % of patients vs only 13 % who received standard medical treatment [84]. In a recent randomized controlled trial, 42 % of obese patients with T2DM who underwent RYGB surgery and 37 % of those who underwent LSG surgery achieved remission of T2DM compared with 12 % of patients treated with conventional medical therapy [85••]. In another recent randomized controlled trial, 95 % of individuals with T2DM who underwent BPD and 75 % of those who underwent RYGB surgery, but none of those who received standard medical therapy achieved remission of T2DM [86••].

The long-term effects of bariatric surgery on T2DM remission were examined in the Swedish Obese Subjects Study (SOS), a nonrandomized prospective case-control study in over 4,000 obese patients who underwent bariatric surgery [87]. They found that 72 % of T2DM patients achieved remission at 2 years after surgery, and 36 % had maintained T2DM remission at 10 years after surgery [87]. Similar results were found in another smaller study which showed durable remission of T2DM (>5 years) in over half of the 89 % of patients who had achieved early following RYBG remission [88], and a meta-analysis which reported that 62 % of patients with T2DM remained free of diabetes for more than 2 years following bariatric surgery [82].

The effect of bariatric surgery (LAGB, VBG, RYGB) on the prevention of T2DM in obese adults was recently examined in the SOS study which followed surgically treated and matched controls for 15 years [89••]. Bariatric surgery compared with standard care reduced the long-term relative risk of T2DM by 78 % in obese adults, and among those with IFG it reduced the relative risk of T2DM by 82 %. The postoperative mortality was 0.2 %, and 2.8 % of patients had complications that required a reoperation [89••]. These findings indicate that bariatric surgery has effective and durable effects on the prevention of T2DM in obese adults, particularly among those with IFG. Randomized controlled trials are needed to confirm whether bariatric surgery is an effective and safe approach for preventing T2DM in high-risk individuals.

Conclusions

T2DM is characterized by a progressive loss of β -cell function that occurs against a background of chronic insulin resistance. The rapid rise in rates of T2DM echoes a similar rise in rates of obesity, which causes insulin resistance and may have additional effects on β -cell health. Interventions that reduce body fat (such as diet and exercise, GLP-1 receptor agonists, or bariatric surgery) or that change fat biology (TZDs) provide the best evidence

for slowing or arresting the deterioration of β -cell function that causes T2DM. These interventions should form the basis of interventions to prevent and treat T2DM, particularly early in its course.

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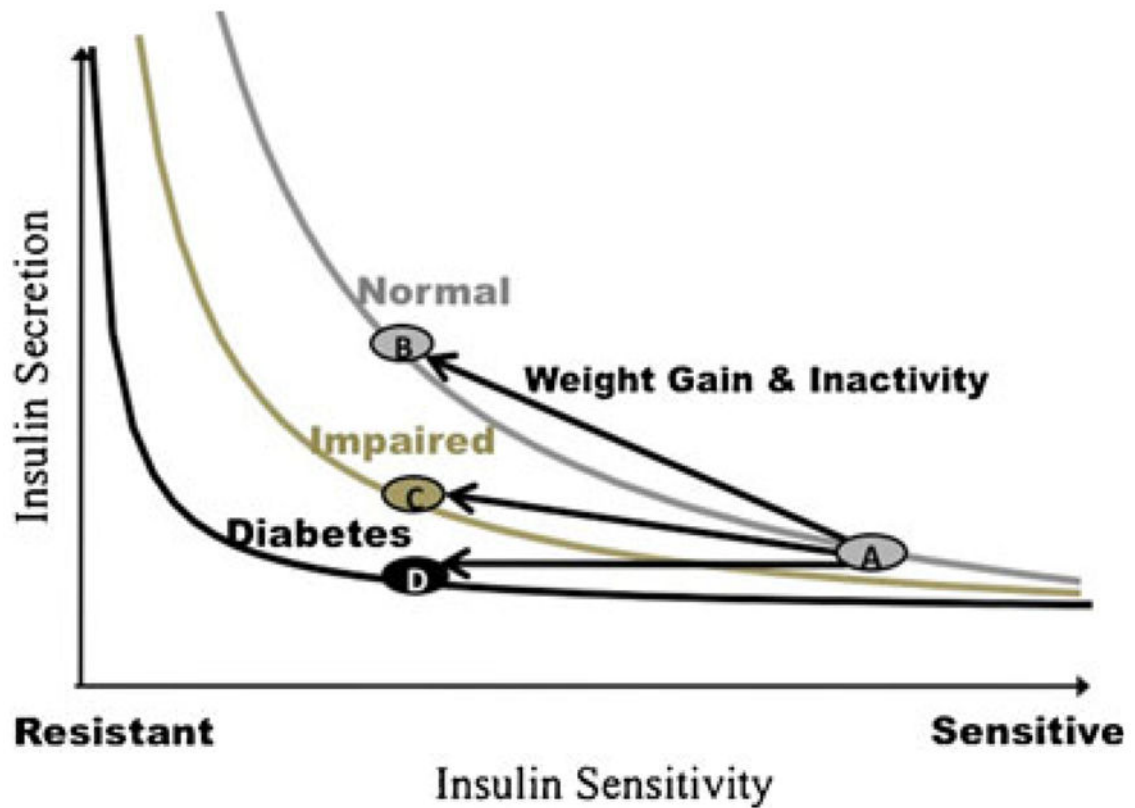


Fig 1.

The Disposition Index (DI) is the product of insulin secretion and insulin sensitivity. Normally, increases in insulin resistance (due to factors such as weight gain and inactivity) are matched by a compensatory increase in insulin secretion in a hyperbolic relationship (A to B) and DI remains constant. Inadequate insulin secretion to compensate for insulin resistance results in a reduction in DI and impaired glucose homeostasis (A to C) and eventually to type 2 diabetes (A to D). (Data adapted from: Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest.* 1981;68(6):1456–67) [9].

Table 1

Summary of diabetes prevention trials

Study	Participants at high-risk for diabetes	Intervention	Relative reduction in risk of diabetes ^a
DPP	IGT	Lifestyle	58 %
Finnish DPS	IGT	Lifestyle	58 %
XENDOS	IGT	Orlistat + lifestyle	45% ^b
TRIPOD	Prior GDM	Troglitazone	55 %
DPP	IGT	Troglitazone	75 %
DREAM	IGT	Rosiglitazone	60 %
ACT NOW	IGT	Pioglitazone	72 %
DPP	IGT	Metformin	31 %
Stop-NIDDM	IGT	Acarbose	25 %

DPP Diabetes Prevention Program, *DPS* Diabetes Prevention Study, *TRIPOD* troglitazone in prevention of diabetes, *DREAM* diabetes reduction assessment with ramipril and rosiglitazone medication, *ACT NOW* Actos now, *IGT* impaired glucose tolerance, *GDM* gestational diabetes mellitus

^a vs placebo and/or usual care

^b vs lifestyle intervention