

## NEW THERAPEUTIC APPROACHES TO PREVENT OR DELAY BETA-CELL FAILURE IN DIABETES

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received: July 25, 2015      accepted: August 25, 2015

available online: September 15, 2015

### Abstract

**Background and aims:** The most recent estimates of International Diabetes Federation indicate that 382 million people have diabetes, and the incidence of this disease is increasing. While in type 1 diabetes mellitus (T1DM) beta-cell death is autoimmune-mediated, type 2 diabetes mellitus (T2DM) results from an interaction between genetic and environmental factors that impair beta-cell function and insulin action. Many people with T2DM remain unaware of their illness for a long time because symptoms may take years to appear or be recognized, while the body is affected by excess blood glucose. These patients are often diagnosed only when diabetes complications have already developed. The aim of this article was to perform a review based on literature data on therapeutic modalities to prevent/delay beta cell function decline. **Material and Methods:** We searched MEDLINE from 2000 to the present to identify the therapeutic approaches to prevent or delay beta-cell failure in patients with T2DM. **Results and conclusions:** Several common polymorphisms in genes linked to monogenic forms of diabetes appear to influence the response to T2DM pharmacotherapy. Recent studies report the role of the G protein coupled receptor 40 (GPR40), also known as Free Fatty Acids Receptor 1 (FFAR1) in the regulation of beta-cell function- CNX-011-67 (a GPR40 agonist) has the potential to provide good and durable glycemic control in T2DM patients.

**key words:** Beta-cell function; Beta-cell failure; GLP-1 agonists; DPP-4 inhibitors; Thiazolidinediones; Pharmacogenetics.

### Background and Aims

IDF's most recent estimates (for the years 2013 and 2035) indicate that 8.3% of adults – 382 million people – have diabetes, and in less than 25 years the number of people with the disease is set to rise beyond 592 million [1]. "The burden of diabetes is reflected not only in the increasing number of people with diabetes, but also in the growing number of premature deaths due to diabetes" [1]. Diabetes caused 5.1 million deaths in 2013 [1].

The consideration of the pancreatic beta-cell as a central player in the pathogenesis of both type 1 and type 2 diabetes has renewed focus on ways to improve glucose control by preserving, and improving the function of this key cell type [2]. However, in T1DM, beta-cell loss occurs as a consequence of immune-mediated beta-cell destruction, while in T2DM beta-cell loss is explained mainly by a significant increase in beta-cell apoptosis [3]. T2DM, the most common form of the disease, is a common condition and a serious global health problem,

characterized by a progressive failure of pancreatic beta-cells in a setting of chronic insulin resistance [4]. T2DM is influenced by lifestyle factors (e.g., obesity, age, pregnancy), but has a strong genetic component. Several genes are considered to be involved, including some encoding for transcription factors, molecules of the insulin signaling pathways, glucose metabolism proteins, each with a little effect on T2DM risk [5].

The two major mechanisms for beta cell replenishment are replication (proliferation) of existing beta cells (beta cell self-replenishment or beta cell replication) and differentiation of new beta cells from non-beta islet cells, pancreatic, and extra-pancreatic cells including stem/progenitor cells (i.e., beta cell neogenesis from non-beta cells) [6,7].

Glucose homeostasis is maintained by the action of insulin (secreted from the pancreatic beta cell) in opposite with glucagon (secreted from the islet alpha cell).

Glucose is the main stimulus for insulin secretion and the glucose-sensing mechanism of the beta cell is essential for maintenance of glucose homeostasis [8].

The aim of this article was to perform a review based on literature data on therapeutic modalities to prevent/delay beta cell function decline.

### **T2DM pathogenesis**

Diabetes is biochemically characterized by an increase in plasma glucose levels. Levels of plasma glucose are determined by the sensitivity of tissues to insulin and by the amount of insulin secreted by the pancreatic beta-cells [9]. Multiple factors, including genetic predisposition, lipotoxicity, glucotoxicity, and decreased beta-cell mass and function are considered to play a role in the pathogenesis of T2DM [9,10]. The genetic background induces insulin resistance and beta-cell failure, while

weight gain and physical inactivity worsen these inherited metabolic abnormalities. Many efforts have been made to elucidate the precise mechanisms by which beta-cell number and function decline in patients with T2DM [9,11].

### ***Beta-cell dysfunction and loss in T2DM***

Two proposed mechanisms for glucotoxicity leading to beta cell loss are endoplasmic reticulum (ER) stress and oxidative stress. Oxidative, Endoplasmic Reticulum (ER) and hypoxic stress, as well as proinflammatory cytokines, are all considered to be involved in beta-cell dysfunction [12]. In response to these stressors, beta-cells can fail to proliferate or undergo apoptosis or uncontrolled autophagy (Figure 1) [11-13]. Emerging evidence also suggests that they can dedifferentiate or transdifferentiate into other pancreatic cell types, a new concept in the pathogenesis of beta-cell dysfunction [14].

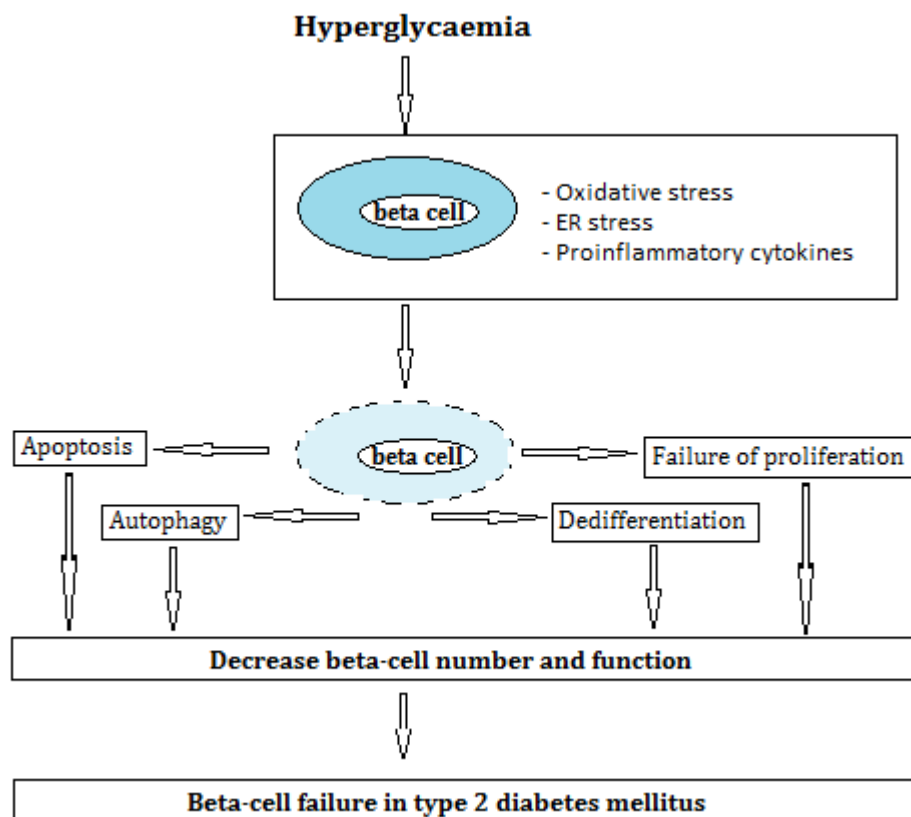
### ***Oxidative stress***

Oxidative stress induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS) is critically involved in the impairment of beta-cell function during the development of diabetes [15] and is also considered to play a large part in the so-called glucose toxicity. Because of their low antioxidant capacity, beta-cells are extremely sensitive to oxidative stress [16]. Elevation of antioxidant defence pathways has the potential to protect pancreatic beta-cells against ROS/RNS-induced cell death and the accompanying loss of function. Therefore, the production and evaluation of drugs that increase the efficacy of antioxidant enzymes or alleviate pathophysiological ROS formation—preferably in a beta-cell specific way—constitute a novel strategy aimed at diabetes prevention/treatment.

Chronically elevated glucose levels lead to irreversible damage of pancreatic beta-cells by oxidative and ER stress, gluco- and lipotoxicity,

as well as proinflammatory cytokines exposure. Beta-cells fail to proliferate, dedifferentiate or have uncontrolled autophagy or apoptosis. These

mechanisms reduce the beta cell number and lead to beta cell dysfunction.



**Figure 1.** The mechanism of beta-cell failure in type 2 diabetes mellitus. (Data adapted from [12]).

### Endoplasmic reticulum stress

Since beta-cells synthesize and secrete large amounts of insulin they have a highly developed ER that is able to synthesize, assemble and fold secretory proteins, and are therefore susceptible to ER stress [17]. ER stress may be important in mediating beta cell apoptosis in response to glucose, lipids, free fatty acids and islet cell amyloid polypeptide [18]. Prolonged ER stress may also lead to the generation and accumulation of ROS (through oxidative protein folding) that can mediate beta cell apoptosis.

Lindahl et al. reported that the mesencephalic astrocyte-derived neurotrophic factor (MANF) is an ER stress-inducible protein, but its physiological role in mammals is not fully known [19]. MANF protein enhanced beta-cell

proliferation in vitro and overexpression of MANF in the pancreas of diabetic mice enhanced beta-cell regeneration [19]. Because MANF is expressed in human beta-cells also, it might have therapeutic potential for diabetes treatment.

### Pro-inflammatory cytokines

An enormous volume of literature has described the toxic effects of the pro-inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor (TNF), and interferon- $\gamma$  (IFN $\gamma$ ), impair beta-cell growth and function *in vitro* [20]. Moreover, Ehses J. *et al.* have reported macrophage infiltration and increased IL-1 $\beta$  expression in the pancreatic islets of patients with T2DM [21]. Recent research shows that beta-cell specific IL-6

expression is linked to spontaneous and virus-induced autoimmune diabetes [22]. The study of Larsen *et al.* showed that IL-1 receptor antagonist –anakinra- improved glycemic control in patients with T2DM, most likely through enhanced beta-cell secretory function [23].

### ***Fatty acid metabolism and lipotoxicity***

Exposure to high levels of saturated free fatty acids (FFAs) also induces  $\beta$ -cell apoptosis, a phenomenon also known as lipotoxicity. Chronic exposure to elevated FFAs or high glucose increases apoptosis in rat pancreatic islets and these cytotoxic effects could be mediated by oxidative stress [24]. This may contribute to the beta-cell failure that occurs in most of the type 2 diabetic patients few years after the clinical diabetes onset [25]. Interestingly, a sustained increase in plasma FFAs levels induces beta-cell dysfunction in patients who are genetically predisposed to T2DM but not in healthy individuals [24]. From a therapeutic perspective, interventions to prevent the development of T2DM may target insulin resistance in adipose tissue in individuals genetically predisposed to develop T2DM.

Sommerweiss *et al.* proved that oleate protects INS-1E beta-cells from palmitate-induced apoptosis by the suppression of ER stress and their results support the potential role of monounsaturated fatty acids (MUFAs) in the therapy of diabetes [26].

### ***Amyloid deposition***

Jurgens *et al.* have demonstrated that islet amyloid deposition in human pancreatic islets is associated with decreased beta-cell area and increased beta-cell apoptosis [27]. They reported for the first time that beta-cell apoptosis is significantly associated with both increased islet amyloid severity and decreased beta-cell area. Amyloid deposits in pancreatic islets are observed in >90% of patients with T2DM and

are associated with reduced beta-cell mass. These findings suggest that interventions aimed at limiting or preventing islet amyloid deposition may have beneficial effects in preserving beta-cell mass in T2DM.

In conclusion, beta-cell dysfunction in T2DM develops via various mechanisms, which lead to increased apoptosis, failure of proliferation, uncontrolled autophagy and dedifferentiation.

### **Effects of T2DM therapies on beta-cell function**

Below, we discuss the actual therapies used in the treatment of T2DM and their effect on beta-cell function, and effectiveness in preventing progression of T2DM. Early introduction of intensive glycemic control, even on a short-term, minimize microvascular complications in patients with T2DM [28].

#### ***Lifestyle intervention***

Obesity is a major risk factor for insulin resistance and T2DM, and the increased prevalence of obesity is largely responsible for the consequent increase in T2DM.<sup>1</sup> Obesity and lack of physical activity induce insulin resistance and increase the workload of beta-cells. Weight loss and exercise interventions increase insulin sensitivity and decrease the secretory need of beta-cells [29]. It is necessary to integrate periodic lifestyle counseling into the treatment program, because lifestyle change is difficult to implement and maintain.

#### ***Pharmacogenetics in Diabetes***

Pharmacogenetics is a scientific discipline that examines genetic variations that give rise to different response to drugs. Monogenic diabetes constitutes a heterogeneous group of single gene disorders. Monogenic diabetes forms can be divided into 2 large groups: resulting from impaired insulin secretion or from an abnormal

response to insulin [30]. Several common polymorphisms in genes linked to monogenic forms of diabetes appear to influence the response to pharmacotherapy. Variation in sulfonylurea (SU) response may be explained by variation in genes involved in regulating beta-cell function [30]. The polymorphisms of *KCNJ11* and *TCF7L2* genes were associated with a therapeutic efficacy of SU in patients with T2DM [31]. However, pharmacogenetic studies on therapeutic response within diabetes remain limited.

### ***Pharmacological intervention***

Preservation of beta-cell function is critical to prevent future development of T2DM [32]. A variety of glucose-lowering agents - incretin mimetics (GLP-1 receptor agonists – GLP-1RA), dipeptidylpeptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZDs)- have been suggested to prevent beta-cell apoptosis, but their long-time effects on beta-cell mass in patients with diabetes remain to be elucidated [33,34].

### ***Incretin-based therapies***

Incretin-based therapies, which have become available within the past 8 years, include glucagon-like peptide 1 (GLP-1) receptor agonists, that mimic the effects of endogenous GLP-1, and DPP-4, that prevent the rapid degradation of the endogenously secreted GLP-1 hormone [35]. Both GLP-1 receptor agonists and DPP-4 inhibitors minimize the risk of hypoglycemia seen with insulin and some oral antidiabetic drugs.

#### ***a) Glucagon-like peptide-1 agonists (exenatide, liraglutide, lixisenatide)***

GLP-1 is an incretin hormone secreted by the L cells in the intestine in response to nutrient stimulation and has a number of properties that make it an ideal agent for the treatment of T2DM. The acute effect of GLP-1 on beta-cell is stimulation of glucose-dependent insulin release [36].

Exendin-4 has homology with the human GLP-1 sequence but has a longer half-life. Synthetic exendin-4 (*exenatide*) was approved for use in the US in 2005 and is administered twice per day by subcutaneous injection [36]. In 2012, a new once-weekly formulation of exenatide was approved. In a recent publication it was suggested that exendin-4 reduced Free Fatty Acids Receptor 1 (FFAR1) levels [37].

*Liraglutide* was approved by FDA in 2010 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and was also recently approved for use in Europe [38]. It can be used as monotherapy or in combination with metformin (MET), a SU, or a TZD with significant improvements in beta-cell function, as measured by homeostatic model assessment (HOMA) and the proinsulin-to-insulin ratio.

*Lixisenatide* is a once-daily prandial GLP-1 receptor agonist for the treatment of T2DM that was granted marketing authorization by the European Medicines Agency (EMA) in February 2013 and it has distinct effects on postprandial blood glucose as a result of slowing down of gastric emptying [39]. Lixisenatide improves both fasting and prandial glycemia with a pronounced prandial effect. This is accompanied by a significant improvement in beta-cell function assessed by HOMA-B, which is in accord with preclinical mechanistic findings with lixisenatide and other GLP-1 receptor agonists [39].

#### ***b) Dipeptidyl peptidase 4 inhibitors***

Dipeptidyl-peptidase (DPP) 4 is a ubiquitous enzyme that is responsible for the inactivation of both incretin hormones GLP-1 and *gastric inhibitory polypeptide* (GIP). DPP 4 inhibitors are Food and Drug Administration (FDA) approved oral medications in type 2 diabetes, which inhibit DPP-4, thereby increasing circulating concentrations of incretin hormones.



They could provide glycemic control with improved islet cell function [40].

Sitagliptin, the first oral DPP-4 inhibitor, was approved by the FDA in 2006, for use as monotherapy or in combination with metformin or TZD, followed in the USA by saxagliptin. Vildagliptin, another DPP-4 inhibitor, was approved in Europe in 2008. In 2011, linagliptin was approved as a single-ingredient product. In 2012, a fixed-dose combination of linagliptin/metformin was also approved. The newest addition to the class of DPP-4 inhibitors is alogliptin. DPP-4 inhibitors may protect pancreatic beta-cells from enhanced apoptosis in animal models of diabetes, and also improve several markers of beta-cell function in type 2 diabetes. Intuitively, a positive influence of DPP-4 inhibitors on islet function may attenuate the inherently progressive nature of beta-cell loss [41].

### ***Thiazolidinediones***

The effects of pharmacological agonists of peroxisome proliferator-activated receptors gamma (PPAR $\gamma$ ) – thiazolidinediones (TZDs) - have been attributed to increased insulin-stimulated glucose uptake in adipocytes, hepatocytes and skeletal muscle cells, and on the other hand, decreased FFA levels and increased lipid storage in adipose tissue [42].

Rosiglitazone and pioglitazone are used in the treatment of patients with T2DM because they decrease hepatic glucose production and preserve pancreatic beta-cell by preventing apoptosis of beta-cells. Despite many beneficial effects of glitazones (metabolic and anti-arteriosclerotic activity), they also exhibit side effects, such as weight gain, edema, increased risk for bone fractures, heart failure and increased risk of myocardial infarction (in the case of rosiglitazone), which have limited the use of these drugs [43]. Rivoglitazone is the

fourth agent in the thiazolidinedione class of antidiabetes drugs and appears to be more potent in its ability to lower glycosylated hemoglobin (HbA1c) levels compared with other thiazolidinediones [44].

### ***Next-generation treatments***

Recent studies reported a possible role of the G protein coupled receptor 40 (GPR40), also known as FFAR 1, in the regulation of beta-cell function [45]. It was reported that chronic treatment of male Zucker diabetic fatty (ZDF) rats (insulin resistant model with elevated blood glucose and FFAs levels) with CNX-011-67 (GPR40 agonist) increased insulin secretion, decreased blood glucose and reduced beta-cell apoptosis without affecting body weight [45]. From this study data it appears that CNX-011-67 could have the potential to provide good and durable glycemic control in type 2 diabetes patients.

Another study provided evidence that activation of GPR40 with CNX-011-67 stimulates glucose metabolism, improve glucose responsiveness and enhances insulin secretion, with the hope that pharmacological activation of GPR40 will prove beneficial for the treatment of T2DM [46].

Burant *et al.* highlighted several treatments in development. One of the topics under discussion was fatty acid elongases, which have been studied due to the association of long-chain fatty acids and their end products with toxicity related to overconsumption of food [47]. TAK-875, a novel highly selective, orally bioavailable GPR40 agonist, significantly improved glycaemic control in patients with type 2 diabetes with a minimum risk of hypoglycaemia. The outcomes show that activation of FFAR1 is a viable therapeutic target for the treatment of T2DM [48].

Tabatabaei *et al.* reported that an alternative pharmacological approach for the control of

diabetes with antioxidants - a combination of Setarud with curcumin and quercetin - might be an appropriate treatment [49].

## Conclusion

According to current data it can be appreciated that beta-cell failure could be

delayed or prevented by attaining and maintaining good glycemic control. It is theoretically possible to inhibit multiple mechanisms by blocking the pathways leading to beta-cell apoptosis, and this is a challenge for the future.

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