



Beta Cell Protection in Type 2 Diabetes - Does It Matter?

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ABSTRACT

Chronic insulin resistance and inexorable decline in beta cell function characterize type 2 diabetes. Current treatment strategies have failed to protect beta cell function as evidenced by several large clinical trials. Unequivocal evidence exists pertaining to the beneficial effects of even minimally preserved beta cell function. Recent studies have provided better insight into the mechanisms of beta cell growth, differentiation and apoptosis. Simultaneously various modifiable factors have been identified, which are responsible for beta cell failure overtime in the natural history of type 2 diabetes. They have opened new vistas of therapeutic interventions to ameliorate the progressive decline in beta cell function.

Insulin resistance, glucotoxicity, lipotoxicity, inflammation and oxidative stress are some of the important determinants of beta cell failure over and above the presumed genetic predisposition. Early and effective treatment should address to all these issues, which would go a long way in restoration of physiological insulin responses in type 2 diabetes.

INTRODUCTION

Chronic insulin resistance and inexorable decline in beta cell function characterize type 2 diabetes.¹ Both these defects are supposed to have genetic components. Notwithstanding the debate; whether one or the other is the primary defect, clinical presentation of the disease is largely dependent on residual beta cell function. It has been consistently demonstrated that even minimally preserved beta cell function is metabolically beneficial. It leads to lower glycosylated hemoglobin values, lower insulin requirement and lesser decompensation on insulin withdrawal, advertently or inadvertently. On the other hand beta cell dysfunction is responsible for the major abnormalities seen in type 2 diabetes.² They include:

- Loss of first phase insulin response to glucose
- Failure to adapt to insulin resistance as evidenced by flattened dose response to IV glucose
- Delayed and blunted insulin response to meals
- Abnormal rapid and ultradian oscillations in insulin levels

ASSESSMENT OF BETA CELL FUNCTION

Beta cell function can be assessed in clinical practice by calculating ratio of the incremental insulin to glucose responses over first 30 minutes of OGTT.³ This is expressed as $\Delta I_{30}/\Delta G_{30}$. Even after adjustment for insulin sensitivity, which can modulate beta cell function; this clearly demonstrates that beta cell function is a more important determinant of glucose disposal. In normal pregnancy there is 2-3 fold hyperinsulinemia as a result of increased levels of placental hormones. However only

2-5% fail and develop GDM. This clearly explains that beta cell dysfunction is important in the pathogenesis of GDM as well. In the UKPDS study, it has been clearly demonstrated that at the time of clinical presentation, majority of type 2 diabetics have lost 50% of their beta cell function. Furthermore, this study has clearly demonstrated that the current paradigm of diabetes management leads to a progressive decline in beta cell function; irrespective of the treatment modality used. Commensurate with this phenomenon, there was little impact on prevention of macrovascular complications.⁴

Immunological markers can predict beta cell failure in type 2 diabetes. GAD antibodies and multiple islet cell antibodies (ICA) present at the time of diagnosis predict future complete beta cell failure. After diagnosis, GAD antibodies persisted in most of the patients. However, ICA development in patients who were negative at the time of diagnosis indicated decreasing beta cell function.⁵

WHAT LEADS TO BETA CELL DYSFUNCTION?

Defects in beta cell growth and/or function are central to the pathogenesis of type 2 diabetes. Intracellular signals that mediate beta cell growth and function include those that mediate insulin and growth factor signaling in other tissues of the body. In normal individuals glucose-stimulated beta cell mitogenesis is responsible for adequate beta cell growth and differentiation. On the other hand FFA inhibits specific signals that inhibit normal glucose stimulated beta cell mitogenesis. It is understandable that protection of beta cell function will have a salutary effect in

reversal of these abnormalities to normal or at least in mitigating its rapid progression.

Type 2 diabetes is characterized by decreased beta cell mass, decreased insulin secretion and amyloid deposits in the islets.⁶ Obviously any attempt to protect the beta cell function is likely to succeed before significant amyloid deposits in the islets. This calls for an early and aggressive strategy to target multiple factors involved in the progressive decline in beta cell function.

Apoptosis (programmed cell death) is supposed to be the reason for the inexorable decline in beta cell function. However this could be an extremely nihilistic proposition. Large body of evidence has accumulated over last decade that there could be several modifiable factors to protect beta cell during the natural history of type 2 diabetes.

Over last several decades, we have come to understand that beta cell dysfunction can be secondary to large number of modifiable factors; notwithstanding a genetic predisposition to its causation. As a natural corollary to this understanding trials like Steno 2 targeted multiple risk factors for intervention and resulted in impressive reduction in macro vascular complications.⁷ This was associated with greater preservation of beta cell function in these individuals.

Modifiable Factors

Several factors have been identified which are responsible for the decline in beta cell function and fortunately many of them are eminently modifiable. They include:

- a. Insulin resistance
- b. Obesity
- c. Sedentary habit
- d. Imprudent diet
- e. Glucotoxicity
- f. Lipotoxicity
- g. Inflammation
- h. Oxidative stress

Insulin Resistance & Beta Cell Dysfunction

Type 2 diabetes is characterized by progressive loss of beta cell function in the presence of chronic insulin resistance. As a natural corollary chronic amelioration of insulin resistance should preserve beta cell function and delay or prevent the onset of type 2 diabetes. Indeed this hypothesis has been substantiated in several small studies using insulin sensitizers, glitazones and metformin. Stabilization of beta cell function has been demonstrated both at the stage of impaired glucose tolerance as well as at the stage of early diagnosis by doing yearly oral glucose tolerance test (OGTT).

In the TRIPOD study treatment with troglitazone reduced the incidence of type 2 diabetes by 55% in high-risk Hispanic women.⁸ The observed beneficial effect lasted for 8 months beyond the trial period and was associated with stable beta cell function over 54 month period.

Women who completed TRIPOD study are followed in PIPOD study to assess the effect of pioglitazone in glycemic control and beta cell protection. The DREAM study is looking at the effect

of rosiglitazone and ramipril separately and in combination on similar end-points.

Attenuation of hyperinsulinemia by selective K-ATP channel opener has been shown to induce beta cell rest and significant improvement in glucose responsiveness.⁹ This was associated with marked improvement in lipid profile, without significantly affecting food consumption or rate of weight gain.

APOPTOSIS VS NEOGENESIS

Beta cell mass is regulated by a balance of beta cell replication and apoptosis, as well as development of new islets from exocrine pancreatic ducts (neogenesis).^{10,11} It remains controversial whether beta cell mass is decreased in type 2 diabetes or for that matter whether there is a truly increased rate of apoptosis. However recent data convincingly suggest that increased apoptosis rather than decreased neogenesis or replication is the main mechanism leading to reduced beta cell mass in type 2 diabetes.¹² It should be logical to elucidate the mechanisms responsible for the increased apoptosis in the islets of type 2 diabetics. Glucotoxicity, lipotoxicity and deposition of islet amyloid polypeptide are important contributors to beta cell apoptosis

GLP-1 analogues by their 'incretin effect' increase proliferation and decrease apoptosis of beta cells, leading to enhanced islet mass and improved beta cell function.¹³ The Proliferative and anti-apoptotic activity of GLP-1 was mediated by Protein Kinase B.¹⁴

Glucotoxicity and Lipotoxicity

It is unlikely that a single aberrant genetic programming could be responsible for the beta cell apoptosis. Our current understanding tells us that type 2 diabetes is a polygenic disorder and is more of a syndrome rather than single specific entity. It is understandable that some common adverse force is exerted relentlessly on beta cell microenvironment.¹⁵ It is common observation that in type 2 diabetes; even though fasting plasma glucose and glycated hemoglobin are normal, the post-prandial levels of glucose are often abnormal. Post-prandial glucose control could be an important determinant in ameliorating the beta cell degeneration.

Chronic exposure of cultured human islets to high glucose and saturated fatty acid Palmitic acid leads to increased markers of beta cell apoptosis and impaired beta cell proliferation. On the other hand monounsaturated fatty acids palmitoleic acid and oleic acid did not affect DNA fragmentation and induced beta cell proliferation.¹⁶ Supplementation of each of the MUFAs prevented apoptosis and improved beta cell proliferation and improved insulin secretion. Presence of MUFA results in incorporation of palmitate to triglyceride stores. It appears that ability to synthesize triglyceride plays an important role in the protection from Lipotoxicity.¹⁷ Palmitate channeled towards triglyceride would be unavailable for inducing beta cell apoptosis.

Glucotoxicity leads to time-dependent irreversible damage to cellular components of insulin production and therefore to insulin content and secretion. There are several steps from insulin gene expression to insulin release into the blood. They include:

- a. Translation in insulin synthesis
- b. Glucokinase gene expression

c. Mitochondrial function

d. Exocytic mechanisms

Glucotoxicity adversely affects all these steps and consequently there is an accelerated apoptosis.¹⁸

Glucotoxicity leads to overexpression of apoptotic genes Bad, Bid and Bik, while expression of the anti apoptotic gene Bcl-2 remains unaffected.¹⁹ Furthermore chronic hyperglycemia leads to increased secretion of interleukin-1; which leads to beta cell apoptosis through a cascade of events involving NFkB activation, FAS upregulation and DNA fragmentation.²⁰ This opens new vistas for pharmacological intervention with interleukin-1 receptor antagonist.

Glucotoxicity resulting in decreased insulin synthesis and secretion is mediated by decreased insulin gene expression.^{21,22} The metabolic lesion responsible for this phenomenon is a posttranslational defect in pancreas duodenum homeobox-1 (PDX-1) mRNA maturation. Absence of PDX-1 in glucotoxic cells leads to impaired transcription of insulin promoter gene. On the other hand transfection of PDX-1 into glucotoxic beta cells, improves insulin promoter activity.¹⁵ Several experiments have shown that treatment with troglitazone, aminoguanidine, phlorizin or N-acetylcysteine preserves DNA binding activity and gene expression of PDX-1 and insulin.^{23,24} This was associated with good glycemic control. On the contrary no beneficial effects were found with a nitric oxide synthesis inhibitor or bezafibrate, a drug that lowers circulating triglyceride but not glucose. The drugs in the former group control hyperglycemia and reduce oxidative stress.

In recent years several animal and human studies are looking at the prospect of early initiation of insulin therapy in type 2 diabetes with a view to protect beta cell function.²⁵

OXIDATIVE STRESS

Chronic hyperglycemia is known to produce chronic oxidative stress through various pathways. This is supported by the observation that high glucose concentrations increase peroxide levels in the islets. In hyperglycemic states excessive generation of ROS occurs as a result of oxidative phosphorylation during anaerobic glycolysis.²⁶ Besides these islets contain very low levels of antioxidant enzyme activities. Naturally increased antioxidant activity within the islet may protect it against the oxidative stress associated with glucotoxicity. Exogenous treatment with antioxidants in vivo in animals has shown to prevent islets from glucotoxicity. As a natural corollary antioxidants could play an important role in the protection of beta cells. Testing more potent antioxidants like N-acetylcysteine and glutathione can circumvent failure of previous studies with antioxidants vitamins.¹⁵

Antioxidants could play a big role in protecting beta cells procured from a cadaveric donor and subsequent intrahepatic transplantation. This is because unhealthy levels of ROS are generated during various steps of hypothermia, exposure to collagenase, physical separation from exocrine tissues and deprivation of adequate oxygenation in the early days post-transplantation.¹⁵

INFLAMMATION

Inflammatory cytokines play a major role in the progressive decline in beta cell function overtime. Glitazones have been shown to attenuate the effects of several inflammatory cytokines, including tumor necrosis factor and interleukin-6.²⁷ Cytokines inhibitors have been directly tested for their ability to protect beta cells. As cytokines mediate their effect through an excess production of oxidizing agents and nitric oxide; addition of antioxidants like superoxide dismutase and catalase can provide added protection. These exciting results in animal studies and small human trials are extremely promising for the future treatment of type 2 diabetes.

Interleukin-1 beta is another inflammatory cytokine, emerging as important target for preventing beta cell apoptosis. Imidazoline compounds have shown promising results by their inhibition of the expression of iNOS, a key element in the IL-1 beta induced apoptotic pathway in pancreatic beta cells.²⁸

In the Nurses' Health Study elevated C-reactive protein was shown to be an independent predictor of type 2 diabetes suggesting the important role of inflammation in the pathogenesis of type 2 diabetes.²⁹

CONCLUSION

Desirability of a proposition depends upon its scientific rationale. However what is more important; is whether it is feasible to translate the proposition to reality in the realm of clinical practice. Newer insights into the mechanisms of beta cell growth, survival and apoptosis has ushered in an era of optimism; where protection of beta cells is a reality by myriads interventions; both non-pharmacologic and pharmacologic. It is imperative for the practicing clinicians to be alive to rapidly accumulating knowledge in this exciting area and use the same judiciously for the ultimate benefit of their patients.

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