Early Use of Insulin for Beta Cell Preservation

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Introduction

Type 2 diabetes is a heterogeneous disorder, characterized by beta cell dysfunction and decreased insulin sensitivity. Presence of amyloid deposits in the islets and decreased beta cell mass are the pathological hallmark of the disease. Several clinical and experimental studies have clearly shown that even minimally preserved beta cell function is metabolically beneficial. This leads to lower HbA1C levels, lower insulin dosage and lesser metabolic decompensation after insulin withdrawal.

Quantitative assessment of beta cell function by hyperglycemic clamp studies has clearly shown that it is the most important determinant of glucose disposal. It has also been found to be a major contributor to oral glucose tolerance even in high risk relatives of type 2 diabetic patients in different ethnic groups. Beta cell function, quantified as the ratio of the incremental insulin to glucose responses over the first 30 minutes during the oral glucose tolerance test (OGTT) was found to be more important in determining glucose disposal. This result was valid even after adjustment for insulin sensitivity, which might modulate beta cell function.

Beta cell dysfunction is responsible for various defects observed in type 2 diabetics, individuals with impaired glucose tolerance (IGT) and those genetically predisposed to develop type 2 diabetes. These defects include:

- Diminished first and second phase insulin release
- Decreased pulsatile or oscillatory insulin release
- Increased release of proinsulin-like molecules and
- Impaired ability to compensate for superimposed tissue insulin resistance.

CAUSES OF BETA CELL DYSFUNCTION

The United Kingdom Prospective Diabetes Study (UKPDS) has clearly shown that irrespective of the treatment modalities used, there was a progressive decline in beta cell function over time. Notwithstanding the genetic predisposition (apoptosis), there are several acquired and reversible factors which can accelerate the beta cell dysfunction. They include:

- Obesity
- Insulin resistance
- Glucotoxicity
- Lipotoxicity
- Inflammation
- Alterations in incretins – Glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP)
- Malnutrition in uterus and in early life, which may affect programming of the beta cells with respect to glucose sensing, apoptosis, regeneration and ability to compensate for IR.
- Functional defect of beta cell, as evidenced by greater than 80% reduction in insulin release with only 20 - 40% reduction in beta cell mass.

RATIONALE OF EARLY INSULIN USE IN BETA CELL PRESERVATION

While several strategies can be employed to tackle many of these factors contributing to beta cell decline, insulin alone has the most salutary effect on majority of them. Both acute and prolonged hyperglycemia adversely affects beta cell function. Glucotoxicity leads to impaired gene transcription, down-regulation of glucose transporters and alteration of transporter function induced by oxidative stress. Early use of insulin results in increased insulin gene expression and insulin synthesis. It provides rest to beta cells, already stretched to their capacity and helps them regenerate over time. Beta cells are most stressed and therefore most vulnerable to programmed cell death (apoptosis) during the first few months following the clinical onset of diabetes. Quick restoration of euglycemia by early insulin therapy at this stage will naturally preserve beta cell function on a long term basis. This has been demonstrated in several experimental and clinical studies.

In Chinese hamster, a spontaneous and selectively inbred animal model for non-obese type 2 diabetics, two weeks of normalization of glycemia resulted in marked improvement in beta cell function. This was characterized by improved beta cell signaling induced by the cyclic AMP protein kinase A pathway. This was also associated with improved islet insulin content and beta cell morphology as demonstrated by immunocytochemistry. In patients with Latent Autoimmune Diabetes of Adults (LADA), early initiation of insulin has been shown to preserve beta cell function. This was evidenced by preserved C-peptide response compared to baseline in insulin treated group, as compared to Sulfonylurea (SU) group, which showed significantly lesser C-peptide after two years. This worsened further at the end of three years. It has also been demonstrated that short term glycemic control by intravenous insulin infusion restores SU sensitivity in significant proportion of non-obese SU non-responsive type 2 diabetic subjects. These patients showed a significant improvement of metabolic control and beta cell secretion. During the 6-month follow up period they could be managed with glibenclamide alone. Metabolic improvement was associated with improvement in fasting and post meal C-peptide levels as well.
A number of in vitro and animal studies have demonstrated that chronic elevation of free fatty acid impairs beta cell function (Lipotoxicity). Free fatty acid (FFA) also antagonizes the action of insulin, both on glucose production and glucose utilization.\(^{10}\) It also promotes Gluconeogenesis and enhanced Glucose 6-phosphatase gene expression, which directly increases glucose production. Increased beta cell concentration of fatty acid co-A, TNF-alpha, resistin, leptin, adipin and amylin and tissue accumulation of lipids all contribute to the inexorable decline in beta cell function.\(^{11}\) Early insulin therapy is known to mitigate the deleterious effects of these molecules directly or indirectly.

**Glucose effectiveness**: In normal individuals glucose is master regulator of the glucose flux in the tissues. In type 2 diabetics, presence of hyperglycemia fails to suppress glucose production and also fails to stimulate glucose utilization. It has been shown that only 3 days of intensive insulin therapy regains normal effectiveness of glucose to suppress glucose production and stimulate glucose utilization in response to hyperglycemia.\(^{12}\) During this study it was concluded that the mechanism through which glucose effectiveness was restored included improved glycogen synthesis and decreased level of circulating FFA.

**Inflammation** has been identified as an important determinant in the pathogenesis of beta cell dysfunction. Several pro-inflammatory transcription factors have been identified which inflict damage to the beta cells through liberation of large numbers of inflammatory cytokines.\(^{13}\)

It has now been established that our daily macronutrient intake is largely pro-inflammatory. It leads to oxidative stress, generation of reactive oxygen species and expression of pro-inflammatory transcription factor NFkB. Resultant liberation of cytokines like, intercellular adhesion molecules-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), p-selectin and others initiate and perpetuate the inflammation induced damage to the beta cells. In the context of macronutrient intake, prompt and adequate insulin response counteracts the expression of NFkB and subsequent inflammatory cascade. This inhibits any inflammation induced damage to the beta cells. Insulin in this respect can be viewed as the natural anti-inflammatory molecule. Elegant studies have shown remarkable reduction in the level of NFkB, ICAM-1, p-47, Reactive Oxygen Species (ROS) etc by insulin administration.\(^{14}\)

**Loss of first phase insulin response (FPIR)** has emerged as one of the most important factor in the pathogenesis of type 2 diabetes. Its magnitude correlates with the degree of beta cell dysfunction.\(^{15}\) Its consequences include:

- Inadequate inhibition of endogenous glucose production.
- Rise in non esterified fatty acids (NEFA) due to inadequate antilipolytic action of insulin.
- Inadequate priming of insulin sensitive tissues leading to decreased glucose disposal.
- Altered signaling capacity of hormones leading to insulin resistance.
- Enhanced stimulatory action of glucagon on gluconeogenesis.
- Enhanced post prandial hyperglycemia.
- Increased risk of micro and macrovascular complications.

It is also important to understand the correlation between levels of glycemia and loss of FPIR:

- FPIR is mostly absent when the FPG is more than 109 mg/dl
- When FPG is > 140 mg/dl 75% of beta cell function is lost.\(^{16}\)
- When FPG is > 180 mg/dl there is complete loss of FPIR.
- When 2 hrs PG values are > 200 mg/dl there is marked reduction in FPIR.\(^{17}\)
- Even in subjects with IGT there is marked reduction in the FPIR.

Considering these facts it seems prudent that all attempts be made to restore FPIR. This would logically correct or mitigate all the consequences mentioned above. Additional benefits would include beta cell rest, reduced hyperinsulinemia of the late phase after ingestion of a meal, reduced production of islet amyloid peptide and improved insulin secretion over time. Excessive accumulation of amyloid deposits between islet cells and capillaries leads to destruction of islet endocrine cells and progressive worsening of beta cell function. Current paradigm of using sulfonylureas (SU) in majority of type 2 diabetic patients leads to increased deposition of amyloid deposits and faster decline in beta cell function.\(^{18}\) However insulin sparing sulfonylureas (Glimepiride) and non-sulfonylureas secretagogues (Repaglinide and Nateglinide) may not produce this undesired effect.

**Conclusion**

Insulin possesses the unique ability to correct majority of the reversible factors contributing to the inexorable decline of beta cell function in the natural history of type 2 diabetes. Early initiation of insulin addresses the issues of glucotoxicity, lipotoxicity, inflammation, first phase insulin response, insulin resistance and many other factors. Backed by solid pathophysiological rationale and evidenced by animal and human studies, it sounds prudent to shift the paradigm of insulin administration in type 2 diabetes from one of 'last resort' to 'first assault'.

**References**


