

β -Cell preservation in Type 2 Diabetes Mellitus, practical?

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Key Words: Diabetes Mellitus, β -Cell, Early Insulin Therapy.

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Introduction

Glycaemic control in Type 2 Diabetes Mellitus (T₂DM) not only improves symptoms and quality of life but also prevents / postpones micro and macrovascular complications. Also from a number of studies, particularly from United Kingdom Prospective Diabetes Study (UKPDS), we now know clearly that T₂DM is a progressive disorder^{1,2}. This needs modification of treatment continuously as the disease progresses. Current clinical management of T₂DM is focussed on treatment of the signs and symptoms of late stages of disease. We discuss intervention on early stage of T₂DM to preserve beta cell function based on a broad understanding of existing data, practice experience and rational speculation³.

β-Cell: Normal Function

The functions of the β-cells are synthesis, storage and release of Insulin. Normal blood glucose is maintained in a healthy individual by a complex interaction of insulin secretion from the pancreas, hepatic glucose output and glucose uptake in the periphery (insulin and non-insulin mediated). Normally we have insulin secretion at the basal condition and in response to a meal. Insulin is secreted in two phases following a meal –

- 1) A fast phase requiring ATP and Ca⁺⁺ in which granules in the "readily released pool" are "docked" and "energized", followed by release from the beta cell. This phase of insulin secretion accounts for only about 5% on the total insulin released after a meal.

2) A slow or second phase also requiring ATP, in which granules are moved from the "reserve pool" to the "readily released" pool of insulin granules. Maximal levels of insulin release are reached after about 60 minutes following a meal.

β -Cell: Abnormality in T₂DM

T₂DM is a combination of Insulin resistance and impaired β -cell function, each one worsening the other, and completing the vicious cycle of progression of T₂DM (Fig.1).

Stages of Type 2 Diabetes

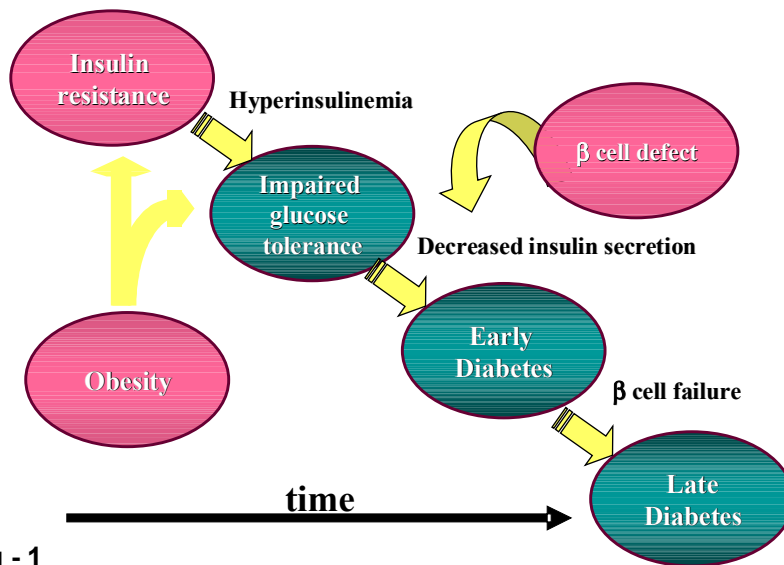


Fig - 1

The earliest discernible abnormality is the impairment in the tissue sensitivity to insulin, resulting in increased circulating levels of insulin. After a certain period when the insulin secretion fails to meet this increased demand, overt diabetes ensues. The earliest abnormality of β -cell in T₂DM is the loss of 1st phase insulin release in response to a meal. This first phase insulin secretion helps in priming the insulin target tissues to maintain normal glucose homeostasis. This abnormality is also an

early manifestation in patients at high risk of developing T₂DM and is found to occur when the fasting plasma glucose level rises to 115-120 mg/dl. Also this defect of insulin release is proportionate to blood sugar level i.e., higher the blood sugar, worse is the defect.

T₂DM -- A Progressive Disorder

Of the two pathogenetic processes, i.e., insulin resistance and β -cell failure, β -Cell failure is mainly responsible for worsening of glycaemic control in T₂DM (Fig.2).

Natural History of Type 2 Diabetes

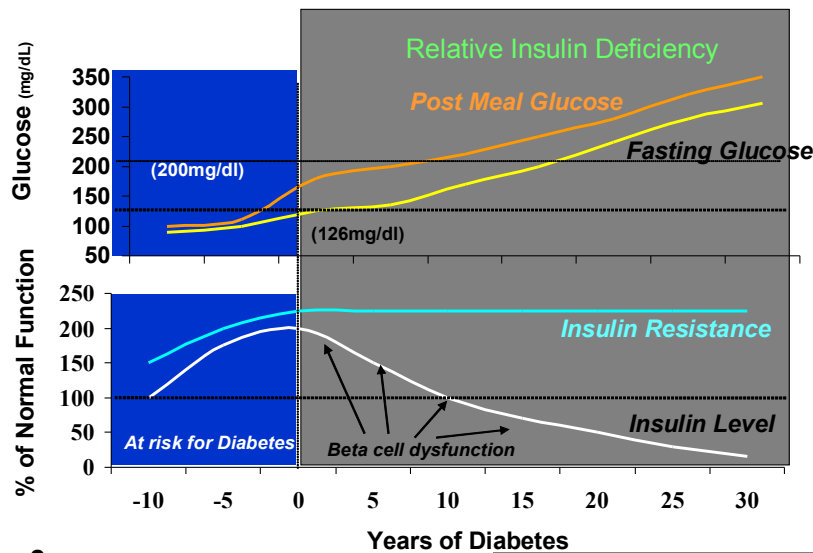


Fig -2

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Results of nine year follow up of UKPDS revealed a steady decline of glycaemic control over the years. This decline was not only with conventional treatment, but also with intensive treatment. The deterioration of glucose control was shown to be associated with diminishing β -cell function as measured by insulin levels and this hyperglycaemia eventually leading to the progression of T₂DM, with the development of micro or macrovascular complications. Not only that, at the time of diagnosis of

T₂DM, 50% of the β -cell function is already lost and the process actually starts 10-12 years before the diagnosis of Diabetes (Fig.3).

Progressive β -cell Failure in T₂DM

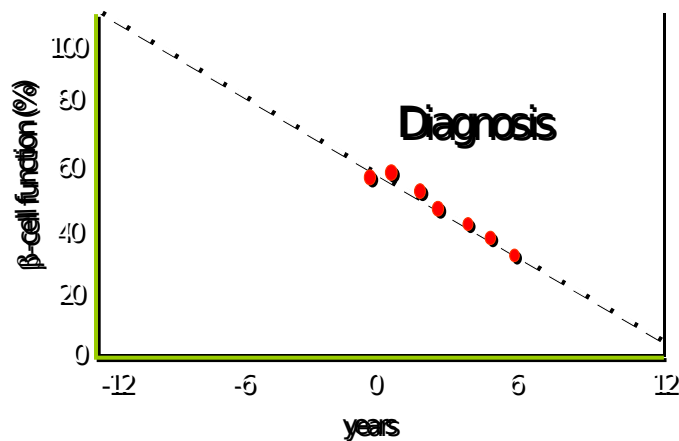


Fig - 3

In an individual case, however, the rate of decline differs depending on the genetic, metabolic and environmental influences. While genetic factors cannot be changed, the modification of environmental factor by therapeutic lifestyle changes like regular exercise, eating healthy food, maintaining ideal body weight and waist hip ratio, moderating alcohol intake have a great role in reducing this rate of decline on the function of β -cells.

The Concept of β -cell Rest/Protection

With fasting plasma glucose of more than 140 mg/dl, more than 75% of the β -cell function is lost. Now at this stage if sulfonylureas are used it would mean whipping the remaining 25% to compensate for the loss of the 75% beta cell function or, in

other words working them to death! This is where the concept of β -cell rest comes in to play. Now by inducing beta cell rest we are serving two purposes-

- 1) Preventing further wear out of the remaining functioning β -cells.
- 2) Delaying the progression of various complications.

Coming to the first point, β -cells can wear out during chronic insulin resistance.

There

is a threshold of work the pancreas can handle beyond which at any particular time, the cells start to deteriorate. What happens here is that, when the body's muscle and fat become resistant to insulin, the β -cells of the pancreas shift into overdrive in order to produce more insulin to compensate for this. Over time this high workload causes the β -cells to wear out. Hyperglycaemia itself worsens β -cell function by direct glucotoxicity. We need to find out what is the most practical and feasible way to stop this wearing out. The UKPDS^{1,2} showed the effect of intensive blood glucose control with either oral hypoglycaemic agents or insulin substantially reduced the risk of diabetic complication in patients with T₂DM. Ten years from the time of diagnosis of T₂DM, there is a significant reduction in complications: 12% for any diabetic related endpoints, 25% for any microvascular endpoints, 16% for myocardial infarction, 24% for cataract extraction, 21% for retinopathy at 12 years, 33% for albuminuria at 12 years^{1,2}. New interventions that stabilize pancreatic beta cell function may have an important impact on length and quality of life, and lead to reduced costs of complications in patients with T₂DM⁴.

Invitro Studies

In health most insulin is secreted in pulses. Patients with established T₂DM have impaired insulin secretion characterised by a defect in insulin pulse mass. In a study done in Hagedron Research Institute, Denmark, it was proved that functional β -cell

rest through intensive treatment with insulin and potassium channel openers preserve residual β -cell function and mass in acutely diabetic BB rats. Here when the β -cells were cultured in a medium with increased glucose concentration (200mg/dl), there was defective insulin secretions (Fig.4). However, when they were transferred to a normoglycaemic culture, β -Cells start back synthesising, storing and secreting insulin normally⁵.

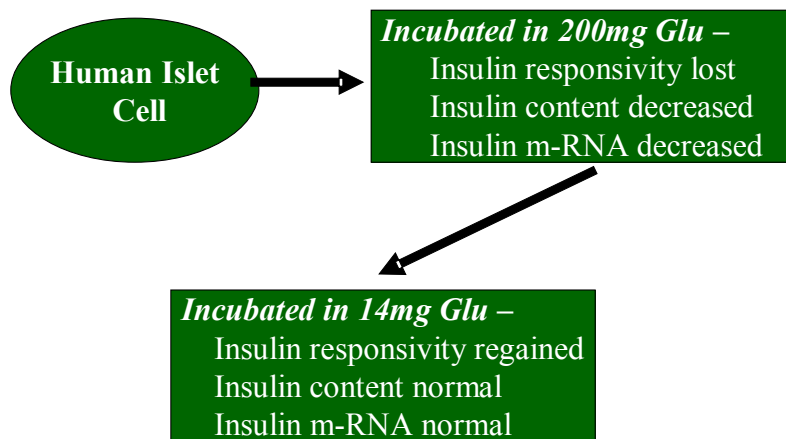


Fig - 4

Robertson RP *J Clin Inv* 1992

There have been a few in vitro studies conducted to show the beneficial effects of antioxidants (probucol, silymarin, bis-o- hydroxyl cinnamoyl methane, gliclazide) and anti inflammatory (heme oxygenase-1, nuclear factor kappaB, lisofylline, carbon monoxide) agents on preservation and improvement in beta cell function^{6,7,8,9}. However there are not many in vivo studies proving the same.

Invivo Studies

Animal Studies

In a study done in Novo Nordisk Lab in Denmark, NN414 an orally active SUR1/Kir6.2 selective potassium channel blocker in comparison with vehicle (V) was used, on chronically diabetic adult male Zucker obese rats. At the end of the treatment period, NN414 and V treated rats had fasting blood sugars of 118mg/dl and 154mg/dl respectively. Fasting insulin levels also differed significantly being 464pM and 767pM in NN414 and V recipients respectively. Rats were then killed and their pancreas perfused in situ for measurement of basal and glucose stimulated first-phase insulin release. Basal insulin was significantly lower and first phase glucose stimulated insulin responsiveness significantly elevated in NN414 versus V pre-treated rats. From this study it was proved induction of beta cell rest would eventually lead to better function of the pancreas later on.

Human Studies

The effect of short-term glycaemic control by intravenous insulin infusion to restore sulphonylurea sensitivity in a group of non-obese uncontrolled T₂DM patients was studied¹⁰. These patients were submitted to a 12-hr intra venous Insulin Infusion to achieve adequate glycaemic control and the responders showed a significant improvement of β -cell function from the second day after the insulin infusion. Not only that, β -Cell function was maintained for more than six months (Fig.5).

Effect of 12-hr Insulin infusion

D Sinagra et al, Diab Care, 2000

N=15, Age at Diag. >35y, Duration >3y,
non-obese, failed to Diet and 15 mg Glib.

	Basal	2days	7days	2mths	4mths	6mths
FBG	201	167	135	146	136	145
C-pep (f) ng/ml	0.56	0.83	x	0.6	0.7	0.46
C-pep (pp)	1	1.46	x	0.86	0.96	0.96
HbA1C	8.3	x	x	6.4	6.5	6.7

Fig -5

This goes on to prove that, not only did the 12-hr Insulin infusion provide long term restoration of the blood glucose levels, they were also able to cause a β -Cell resensitization to sulphonylurea action and maintain normoglycaemia for longer periods than expected¹⁰.

The Kumamoto study involved a relatively smaller number of T₂DM patients (n=110) who were non-obese and only slightly insulin-resistant, requiring less than 30 units of insulin per day for intensive therapy. Over a 6-year period it was shown that intensive insulin therapy, achieving a mean HbA1c of 7.1%, significantly reduced microvascular endpoints compared with conventional insulin therapy achieving a mean HbA1c of 9.4%^{11,12}.

Buchanan et al. tested whether the demands placed on β -cells could prevent T₂DM in people with recent gestational diabetes¹³. In this study 235 young Latinas with gestational diabetes in the recent past were given Troglitazone or a placebo on a daily basis. They postulated that by lessening the work load on the β -cells would keep them

from failing, thereby preventing diabetes. During the 30-month trial, women in the placebo group were diagnosed with diabetes at a rate more than 12% per year as against women taking Troglitazone per 5% a year. This fits the idea that β -cells can wear out through chronic insulin resistance. The woman who's β -cells worked hardest at the start of the study had the greatest benefit from the drug; this was because β -cells got the most 'rest' during treatment¹³.

Maintaining near-normal glycaemia should at least reduce the rate of loss of β -cell and the late complications of central obesity. In the above-mentioned studies it has been proved that early initiation of intensive therapy with Insulin at least for a short duration is helpful to preserve and improve the β -cell function in T₂DM. Even using Insulin for 12 hours as continuous infusion does anything extra than controlling sugar in T₂DM. How is this Insulin doing this job then? Is it because of avoiding the deposition of Amylin (Sulfonylureas increases Amylin which has been shown to enhance β -cell decay) or additional role of Insulin like we have seen in Digami trial¹⁴? Whatever the reason, it seems the balance is towards Insulin.

Conclusion

In view of the development of alternate routes of Insulin administration, it looks certain that the concept of beta cell preservation would get more priority in research and clinical practice. Insulin therapy may become an option as first-line drug therapy very early in the course of the disease and hopefully, will be acceptable by both patients and physicians. Also, it is a reminder for all of us to make early diagnosis of the disease, probably even before blood sugars are high at the expense of hyperinsulinaemia. However, before we recommend early Insulin therapy in T₂DM,

we clearly need long-term intervention trials to determine how best β -cell function can be preserved in the earlier stages of T₂DM. Karvestedt L has shown initial therapy with Insulin for the preservation of β -cell function is successful, but the initial effect does not last on continuing Insulin in T₂DM¹⁵. Does this mean we have a scope of early intermittent treatment with Insulin in T₂DM?

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