Insulin Therapy at Onset of Type 2 Diabetes Mellitus – A New Concept

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Abstract

In this study, insulin therapy was initiated at onset of disease in patients whose fasting blood glucose was more than 250mg/dl. All enrolled subjects were treated with human premixed insulin (30/70) administered subcutaneously twice daily before breakfast and before dinner. A total of 113 subjects entered the study fulfilling the inclusion criteria. Good glycaemic control was achieved in a few days. The dosage requirement of insulin came down gradually and the dosage was set by the patients to maintain HbA1c below 7%. Thus insulin therapy at onset provides an opportunity to correct the glucose tolerance and prevent the complications. Such timely intervention provides long term benefits, laying the foundation for the concept of beta cell preservation rather than only replacing beta cell function. Hence we propose that all patients with type 2 diabetes should be offered insulin therapy at the onset of their diabetes for a period of 2-4 weeks.

The discovery of insulin in 1922 brought in a remarkable change in the outlook for both type1 and type 2 diabetic patients who started surviving for longer periods till they developed vascular complications or infections. The initial preparations of insulin were crude extracts and had several impurities and the volume of injections administered was large and frequent doses were required. Allergic skin reactions and lipodystrophy were common and hypoglycemia was a frequent problem. These problems were gradually overcome by improvements in the purification techniques.

The development of oral hypoglycemic agents around mid 1950s provided an option to the physicians as well as the patient to use either oral medication or to continue insulin. Often oral hypoglycemic agents were preferred. Several workers also attributed the development of the macro vascular complications to insulin usage, suggesting that insulin was atherogenic. This was the topic of debate for several years till it was finally disproved by large scale studies like the UKPDS.

Due to these factors and also the problems associated with injecting insulin, it was not the preferred choice of therapy. Hence, the issue of when and how early to initiate insulin in patients with type 2 diabetes has remained an area of great debate even till now. Clinicians and the patients are reluctant to initiate insulin therapy in patients with type 2 diabetes due to several barriers which exist.

However recent developments and newer knowledge has brought in a change in these concepts. The data from the DCCT2 and the UKPDS trials have brought out the importance of tight metabolic control in arresting the progression of the complications as well as preventing the complications. We have a better understanding of the aetiopathogenesis of type 2 diabetes. There are two main defects the development of insulin resistance and impaired beta cell function. We know that both genetic and environmental factors like life style changes have a major impact on both these defects. We have also learnt that insulin resistance starts initially and gradually increases over a period of time then it plateaus off while the beta cells initially compensate for the insulin resistance by increasing insulin secretion, later when the beta cells get exhausted, the insulin secretion starts declining progressively resulting in hyperglycaemia. At the time of diagnosis of diabetes 50% of the function of beta cells is already lost. We have also a better understanding of the natural history of diabetes. This newer knowledge has provided us to plan our treatment strategies in a rational manner. The UKPDS study has also provided answers to some of the unanswered questions, does insulin or sulphonylurea therapies have any specific advantage or disadvantage. It was shown that blood glucose control is the key to the reduction of the complications and all means of achieving it have the same effect. Intensive insulin therapy does not produce any adverse effect on microvascular or macrovascular complications or the quality of life.

Recent follow up studies on intensively treated subjects of DCCT and UKPDs have shown the benefits of initial tight metabolic control are carried forward for another 10 years even though the control of diabetes was not so intense. This has been called as the ‘metabolic memory’ or ‘legacy effect’. This is a compelling reason to effectively control hyperglycaemia from the time of diagnosis of diabetes.

Research in animal models and in patients with diabetes has shown that glucose toxicity due to the hyperglycaemia contributes to both insulin resistance and beta cell impairment in animal models chronic hyperglycaemia is shown to lower beta cell mass through the induction of apoptosis. It has been shown that short bursts of hyperglycaemia blunt the insulin stimulated glucose uptake resulting in increased insulin resistance. It has also been demonstrated that correction of this hyperglycaemia with use of insulin, improves the insulin sensitivity. Acute hyperglycaemia also has an inhibitory effect on the beta cell insulin secretion (glucotoxicity). High levels of circulating free fatty acids, seen with the hyperglycaemia also cause suppression of beta cell insulin secretion (lipotoxicity). Insulin therapy corrects both the lipotoxicity and glucotoxicity. Even short term insulin therapy appears to result in long term improvements in blood glucose control especially when administered in early stages. Insulin therapy offers several benefits. It improves beta cell function.
by correcting the glucotoxicity and lipotoxicity. It reverses the insulin resistance and imparts beneficial effects on the lipids. Insulin is anti-inflammatory. Overall it also improves the quality of life. Hence it addresses all the pathogenetic mechanisms playing a role in the development of type 2 diabetes. Therefore there is a rationale and role for insulin in the treatment of type 2 diabetes. It can control hyperglycemias in all cases when administered in appropriate dose.

Based on these observations some workers have advocated initiating insulin therapy early in the course of type 2 diabetes in an attempt to preserve beta cell function and improve long term glycaemic control.13

**Material and Methods**

We conducted a study in which insulin therapy was initiated at onset of disease in patients whose fasting blood glucose was more than 250mg/dl. The inclusion criteria were i) diagnosis of diabetes established by the WHO criteria ii) detection of diabetes < 1 month from the date of presentation. iii) severe hyperglycemia at presentation with fasting plasma glucose > 250 mg/dl. The exclusion criteria were as follows i) presence of diabetic ketoacidosis or hyperosmolar non-ketotic coma at presentation or in the past 3 months, ii) presence of acute myocardial infarction, stroke, trauma or active infections iii) not willing to take insulin or comply with the follow up.

All patients meeting the above criteria were enrolled into the study and they were given dietary advice which included the caloric intake provided as per the ideal body weight and activity, advice regarding exercise which emphasized the need for regular physical activity for 30-45 min /day to be started after at least one week of therapy with insulin. All enrolled subjects were treated with human premixed insulin (30/70) administered subcutaneously twice daily before breakfast and before dinner.

The insulin therapy was continued until optimal glycaemic control was achieved or patients developed hypoglycaemia and subsequently they were either continued with diet, exercise and OHA.

**Results**

Patients with type 2 diabetes registered in the clinic from March 1994 – 2000 were 9980. Of these 113 cases fulfilled these criteria, of these 38 cases (33.62%) did not come for 1st follow up (non acceptors / drop out 5) Number of patients who came for follow up was 75 (66.38%) of these long term follow up of more than 1 year was in 24 (32%).

Good glycaemic control was achieved in a few days. The dosage requirement of insulin came down gradually after control was achieved as manifest by hypoglycaemia – leading to withdrawal of insulin. Some of them were managed with diet and exercise alone others required small doses of OHA. There were no cases of secondary failure to OHA. 10 cases are on average duration of follow up of 10 years. 2 cases are under good control with diet and exercise alone, 7 on treatment with oral hypoglycemic agents and one of them requiring insulin to maintain HbA1C below 7%.

**Discussion**

Initiation of insulin therapy at onset results in good glycaemic control with rapid correction of glucotoxicity. The beta cell function is preserved and secondary failure to OHA is prevented with correction of glucotoxicity. There is improvement in both endogenous insulin secretion and insulin sensitivity. This is in contradistinction to the observations in UKPDS where it was found that there is a continuous decline in beta cell function with on going need for additional therapy. Therefore such therapy may be extremely cost effective because of anticipated improvements in long term outcomes resulting in remission/cure.

Ikova et al in 1997 demonstrated that induction of euglycaemia using intensive insulin therapy at the time of clinical diagnosis of diabetes could lead to a significant increase in the insulin secretion and action and thus alter the clinical course of disease.16 They treated 13 newly diagnosed cases unresponsive to diet and exercise with CSII for 2 weeks followed up with treatment with diet alone. 9 patients retained good control with diet alone for 9 to 50 months (26 ± 4.8) while 4 cases were therapeutic failures. They concluded that a significant proportion of type 2 diabetes who fails to respond to dietary measures, short term IIT can effectively establish responsiveness and achieve long term glycaemic control without any medication. They demonstrated a 6 fold increase in glucose disposal, an increase in C-peptide secretion and improved insulin sensitivity.16

Sahay BK et al also reported that insulin therapy at onset in patients with severe hyperglycemic without associated infection, myocardial infarction and other stressful situations led to good glycaemic control quickly and produced long term glycaemic control with only lifestyle measures or small doses of OHA. They concluded that in newly diagnosed type 2 diabetes with elevated fasting glucose levels a 2 – 3 weeks course in intensive insulin therapy can successfully lay a foundation for prolonged good glycaemic control.

Alvarsson et al. in their study of 39 patients with type 2 DM diagnosed 0–2 years, who were randomized to either two daily injections of premixed 50% soluble and 70% NPH insulin or glibenclamide (3.5–10.5 mg daily).18 They were followed up for 2 years. C-peptide– glucagon tests were performed yearly in duplicate after 2–3 days of temporary withdrawal of treatment. Early insulin versus glibenclamide treatment in type 2 diabetes temporarily prolongs endogenous insulin secretion and promotes better metabolic control.

Scarlett et al demonstrated that two weeks of insulin therapy reverses the insulin resistance and improves the insulin mediated glucose disposal by six fold. Insulin provides benefits beyond glycaemic control, improves beta cell function, reverses IR has beneficial effects on lipids.19 They showed that short term insulin therapy can induce long term glycaemic control in newly diagnosed type 2 diabetics with severe hyperglycemia. Recently similar studies were conducted by two groups in China.

In another study by Chen et al newly diagnosed type 2 diabetic patients with severe hyperglycemic were hospitalized and treated with IIT for 10-14 days and randomized to received either insulin or oral antidiabetics.20 They were reassessed at 6 months and one year. HbA1C and beta cell function were better in the insulin treated group. After 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycemic control and significant improvement of β-cell function in new-onset type 2 diabetic patients with severe hyperglycemia. Therefore evidence has emerged that short-term intensive insulin therapy in newly diagnosed type 2 diabetes could improve glycemic control associated with improved insulin secretion.

Weng et al studied the effect of intensive insulin therapy on beta cell function and glycaemic control in patients with newly
diagnosed type 2 diabetes. 21 382 patients were randomized to CSII, MDI or OHA 2 weeks later followed up with diet and exercise. More patients in the insulin groups achieved target glycemic control in shorter time 97.1% in 4 days 95.2% in 5 – 6 days Vs 83.5% in 9.3 days. The remission rates were higher in the insulin treated groups 37.1% and 44.9% Vs 26.7% in OHA (p=.0.012). 21

Thus insulin therapy at onset provides an opportunity to correct all the underlying pathogenic mechanisms i.e. glucotoxicity, lipotoxicity and prevents beta cell apoptosis and suppresses inflammation, leading to beta cell protection. Such timely intervention provides long term benefits, laying the foundation for the concept of beta cell preservation rather than only replacing beta cell function. Hence, we propose that in patients with type 2 diabetes should be offered insulin therapy at the onset of their diabetes for a period of 2-4 weeks.

References


