# Early Insulin Therapy in Type 2 Diabetes

**Ajay Kumar**

## Introduction

Type 2 diabetes is characterized by progressive decline in pancreatic beta cell function and persistent insulin resistance. Decreased beta cell mass and amyloid deposits in the islet are the pathological hallmark of the disease.[1] Preserved beta cell function is the most important determinant of glucose disposal, even after adjustment for insulin sensitivity, which might modulate beta cell function.[2] Besides, beta cell dysfunction is also responsible for several functional abnormalities in type 2 diabetes.[3] These defects include:

- Impaired first and second phase insulin response.

- Decreased pulsatile and oscillatory insulin response.

- Increased release of Pro-insulin like molecules

- Impaired ability to compensate for superimposed insulin resistance

Notwithstanding the genetic predisposition, several environmental and reversible factors are clearly incriminated in the pathogenesis of the inexorable decline in beta cell function. These include:

- Glucotoxicity

- Lipotoxicity

- Inflammation

- Obesity

- Insulin resistance

- Alterations in Incretins- GLP-1 (Glucagon like peptide-1) and GIP (Gastric inhibitory peptide).

- Malnutrition in uterus and in early life, affecting programming of beta cells with respect to glucose sensing, apoptosis, regeneration and ability to compensate for insulin resistance.

- Functional defect of beta cells as evidenced by greater than 80% reduction in insulin release with only 20-40% decrease in beta cell mass.

While several strategies could be employed to tackle many of these factors contributing to beta cell decline, insulin alone has the most salutary effect on most, if not all of them. It is also imperative to appreciate that almost all these factors inflict damage to beta cells several years before the clinical onset of the disease. As a natural corollary, any effort to preserve beta cell function has to be instituted as early as possible in the natural history of the disease.[4] In the current treatment paradigm patients spend 5 years or more with a glycosylated hemoglobin over 8% before decision to start insulin is made. This has been shown by the Kaiser Permanente group

in California that number of patients with HbA1c over 8% on diet, SU, Metformin and combined oral therapy moving to next level of therapy is a meager 66.6%, 35%, 44% and 18% respectively. This is clearly unacceptable and warrants a more proactive approach. Consensus statement of American Diabetic Association (ADA) and European Association for Study of Diabetes have emphasized upon this new treatment paradigm.[5]

Early initiation of insulin addresses the issues of glucotoxicity, lipotoxicity, inflammation, insulin resistance, first phase insulin response and many others. Backed by incontrovertible pathophysiological rationale and evidenced by elegant 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'.

## Rationale for Early Insulin Therapy

Both acute and prolonged hyperglycemia adversely affects beta cell function[6]. Glucotoxicity leads to impaired gene transcription, down regulation of glucose transporters and alteration of transporter function induced by oxidative stress.[7] Early institution of insulin therapy results in increased insulin gene expression and insulin synthesis. It provides rest to the 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 the disease. 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 bred animal model of non-obese type 2 diabetes, 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 improved beta cell morphology as demonstrated by immunocytochemistry.[8] In patients of 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 lesser C-peptide after two years of treatment.[9] This worsened further at the end of three years. It has also been demonstrated that short term glycemic control with intravenous insulin infusion restores SU sensitivity in significant proportion of non obese SU non-responsive type 2 diabetic subjects. These patients showed significant improvement in metabolic control and beta cell function. During the 6 months follow-up period they could be managed with Glibenclamide alone. Metabolic improvement was associated with improvement in fasting and post-meal C-peptide responses as well.[10]

Chronic elevation of free fatty acids (FFA) impairs beta cell function (lipotoxicity). This has been demonstrated in several in vitro and animal studies. Free fatty acid (FFA) also antagonizes the action of insulin, both on glucose production and glucose utilization.[11] It also promotes gluconeogenesis and enhanced Glucose 6 phosphatase gene expression, which directly increases glucose production. Besides, increased concentration of beta cell fatty acid co-A, TNF alfa, Resistin, Leptin, Adipsin and Amylin and tissue accumulation of lipids all contribute to the inexorable decline in beta cell function.[12] Early insulin therapy is known to mitigate the deleterious effects of these molecules directly or indirectly.

## Glucose Effectiveness

In normal individuals glucose is the master regulator of glucose flux into the tissues. In type 2 diabetes, 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 restores normal effectiveness of glucose to suppress glucose

production and stimulate glucose utilization in response to hyperglycemia. During this study it was concluded that the mechanism involved in restoration of glucose effectiveness was improved glycogen synthesis and decreased level of circulating free fatty acids.[13]

## Inflammation

Inflammation has been identified as one of the major determinants of beta cell dysfunction. Several pro-inflammatory transcription factors have been identified which inflict damage to beta cells through liberation of large number of inflammatory cytokines.[14] It has now been established that our daily macronutrient intake is largely pro-inflammatory. It leads to oxidative stress, generation of reactive oxygen species (ROS) and expression of pro-inflammatory transcription factor NFkB. Resultant liberation of cytokines like, Intercellular adhesion molecule-1 (ICAM-1), Vascular cell adhesion molecule-1 (VCAM-1), p-selectin and others initiate and perpetuate the inflammation induced damage to 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 beta cells. In this context insulin can be viewed as a natural anti-inflammatory molecule. Elegant studies have demonstrated remarkable reduction in levels of NFkB, ICAM-1, P-47, ROS etc by insulin administration.[15]

## First Phase Insulin Response (FPIR)

Loss of first phase insulin response has emerged as one of the most important factors in the pathogenesis of type 2 diabetes. Its magnitude correlates with degree of beta cell dysfunction.[16] Its consequences include:

- Inadequate suppression of endogenous glucose production
- Rise in non-esterified fatty acids (NEFA) due to inadequate anti lipolytic action of insulin

- Inadequate priming of insulin sensitive tissues leading to decreased utilization of glucose.
- Altered signaling capacity of hormones leading to insulin resistance
- Enhanced stimulatory action of Glucagon on neoglucogenesis
- Enhanced post prandial hyperglycemia
- Increased risk of micro and macro vascular complications

It is also important to understand the correlation of degree of glycemia and loss of first phase insulin response.

- FPIR is mostly absent when fasting plasma glucose is > 109 mg/dl
- When fasting plasma glucose is more than 140 mg/dl, 75% of beta cell function is lost[17]
- When fasting plasma glucose is more than 180 mg/dl, there is complete loss of FPIR
- When 2 hrs PG values are more than 200 mg/dl, there is marked reduction in FPIR[18]
- Even in subjects with IGT, there is marked reduction in FPIR

Considering these facts it seems prudent that all efforts be made to restore the FPIR. This would logically correct or mitigate all the deleterious consequences mentioned above. Additional benefits will include adequate beta cell rest, reduced hyperinsulinemia of the late phase after ingestion of meal, reduced production of islet amyloid peptide and improved insulin secretion overtime. Excessive accumulation of amyloid deposits between islet cells and capillaries lead to destruction of islet endocrine cells and progressive worsening of beta cell function. Current paradigm of using SU in majority of type 2 diabetics for pronged period leads to increased deposition of amyloid and faster decline in beta cell function.[19] However insulin – sparing SU, Glimepiride and non-sulfonylurea insulin secretagogues, Repaglinide and Nateglinide may not have this deleterious effect.

Marked improvement in glucose tolerance by restoration of FPIR by intravenous infusion of insulin during the first 30 minutes of OGTT has been elegantly demonstrated by Bruttomesso et al. It was clearly demonstrated in this study that neither continuous infusion of insulin nor delaying the infusion beyond 30 minutes achieved similar results.[20] This implies the importance of timing of insulin administration. Unfortunately intravenous insulin infusion cannot be recommended as a therapeutic option for obvious reasons. However rapid acting insulin analogs, Lispro, Aspart and Glulisine have similar pharmacokinetic profile and can mimic intravenous insulin infusion demonstrating similar benefits. Several studies have demonstrated these effects thus assuring translation of the benefit of restoration of FPIR in clinical practice. As compared to regular insulin rapid acting analogs peak earlier (60 versus 120 minutes) and lead to 46% lower glucose area under the curve. These differences could be attributed to rapid and complete suppression of endogenous glucose production as rates of appearance of ingested glucose remains identical. These studies have shown that restoration of FPIR by intensive insulin treatment leads to improved insulin secretion and long term glycemic control.[21] This may pave way to withdrawal of insulin for several years.

Pulmonary delivery of insulin has added another dimension to insulin administration particularly with respect to rapid onset of action. This could have a salutary effect on restoration of FPIR along with ease of administration. Their onset of action is similar to rapid acting analogs while the duration of action is closer to that of regular insulin.[22] Thus their therapeutic effect can be positioned somewhere between the rapid acting analogs and regular insulin. Unfortunately the only FDA approved brand Exubera has been withdrawn from the market due to reasons other than safety.

## Conclusion

Insulin possesses the unique ability to correct majority of the reversible factors contributing to the inexorable decline in beta cell function in the natural history of type 2 diabetes. Initiation of insulin early after clinical onset of the disease provides adequate rest to beta cells and helps restore FPIR. Appropriate timing of insulin initiation and prudent selection of rapid acting insulin analogs and inhaled insulins are extremely vital in preservation of beta cell function, long term glycemic control and prevention of micro and macro vascular complications.

Increasing availability of Incretin mimetic, GLP-1 analogs and DPP IV inhibitors have added exciting dimensions and require better understanding of positioning these molecules in the treatment paradigm for type 2 diabetes. They increase insulin secretion in a glucose dependent manner. It has been demonstrated that they improve insulin responses during 30 minutes immediately after the ingestion of a standard test meal resulting in 58% decrease in the glucose area under the curve.[23] They have several ancillary advantages including weight loss, glucagon suppression and beta cell preservation.[24] In patients with adequate beta cell reserve they could be better option than rapid acting insulin analogs. However these conjectures need to be proven by well designed clinical trials. A very recent report issued on behalf of FDA in October 2007 has linked GLP-1 mimetic Exanetide with episodes of pancreatitis. This may be an area of concern.

High economic burden associated with these newer molecules and strategies will need to be addressed by the health care providers across the globe. In the meantime clinicians must shed the inhibition of starting insulin early, when it is most required. In clinical practice insulin initiation when fasting plasma glucose is more than 140 mg/dl is justifiably warranted as 75% of beta cell function is lost at this juncture. Whipping 25% of tired beta cells to achieve normoglycemia by using drugs like sulfonylureas is unphysiological and does not address the underlying pathogenesis.[16] Similarly decision to start basal or combined basal prandial insulin regimens can be made on the basis of HbA1c

levels between $> 7\% - < 10\%$ or $> 10\%$.

There are several advantages of using this strategy including quick restoration of normoglycemia, restoration of FPIR, beta cell protection, re-establishment of diet responsiveness etc to name a few. All these benefits accrue with transient intensive treatment and small total daily dose of insulin (0.6 units / kg) which is less than the endogenous insulin production in non diabetics.[21] Patient's inhibitions regarding insulin injections should not deter clinicians from prescribing appropriate drug at the right time for the right indication.

## Summary

The current paradigm of management of type 2diabetes is one of sequential addition of treatment modalities starting from medical nutrition therapy, exercise, single or combination oral hypoglycemic agents (OHAs) and finally insulin administration with or without OHAs. This strategy has miserably failed in achieving recommended glycemic goals to prevent micro vascular as well as macro vascular complications. Besides it does not address the fundamental issues of progressive beta cell dysfunction and several other pathogenetic mechanisms including first phase insulin response, inflammation, glucotoxicity, lipotoxicity, inflammation etc. Patients continue to have glycosylated hemoglobin over 8% for more than 5 years before appropriate treatment decisions are made.

Insulin administration is uniquely suitable to address most of these issues, provided it is started early in the natural history of type 2 diabetes. Short-term intensive insulin administration quickly restores normoglycemia, provides rest to the stressed beta cells, allowing them to regenerate and helps in maintaining long term glycemic control with diet, exercise and insulin sensitizers. It also prevents deposition of islet amyloid which is inherent with sulfonylureas administration, the most prescribed drug in the treatment of type 2 diabetes.

Rapid acting insulin analogs are uniquely positioned to address the issues of first phase insulin response and post prandial hyperglycemia. Nasal insulin, GLP-1 analogs and DPP IV inhibitors are potential agents to compete with these drugs. However all of them have one or the other problems of cost, availability, safety and lack of long term data. Notwithstanding patient's and clinician's reluctance to start insulin at the appropriate time, scientific evidence is loaded in favor of using insulin as first assault rather than last resort.

## References

1. Hoppener JWM, Ahren B, Lips CJM. Islet amyloid and type 2 diabetes mellitus. *N Eng J Med* 2000; 343: 411-419.

2. Jensen CC, Cnop M, Hull R L et al for the American Diabetic Association GENNID study group. *Diabetes* 2002; 51: 2170-2178.

3. Jerich JE, Smith TS. Beta cell defects and pancreatic abnormalities in type 2 diabetes mellitus. In: Pickup JC, Williams G Eds Textbook of diabetes, Third edition, Massachusetts, USA Blackwell Publishing Company 2003: 23.1-23.11.

4. Elder R, Stern E, Milicevic Z, Raz I. Early use of insulin in type 2 diabetes. *Diabetes Res Clin Pract* 2005; 68 (Suppl 1): 530-535.

5. Nathan D M, Buse J B, Davidson M B et al. Management of Hyperglycemia in Type 2 Diabetes: A Consensus algorithm for the initiation and Adjustment of Therapy. A Consensus statement from the American diabetic association and the European association for the study of Diabetes. *Diabetes Care* 2006; 29: 1963-1972.

6. Meyer J, Sturis J, Katshchinski M et al. Acute hyperglycemia alters the ability of normal beta cell to sense and respond to glucose. *American J physiol Endocrinol Metabol* 2002; 282: E 917-922.

7. Yki Jarvinon H. Glucose toxicity. *Endocrine Rev* 1992, 13: 415-431.

8. Kohnert KD, Hehmke B, Kloting I et al. Insulin treatment improves islet function in type 2 diabetic Chinese hamsters. *Exp Clinical Endocrinol Diabetes* 2001; 109: 196-202.

9. Kobayash T, Nakanishi K, Murase T et al. Small doses of subcutaneous insulin as a strategy for preventing slowly progressive beta cell failure in islet cell antibody positive patients with clinical features of NIDDM. *Diabetes* 1996, 45; 622-626.

10. Sinagra D, Greco D, amato MC et al. A 12 hour intravenous insulin infusion restores the beta cell response to sulfonylureas in patients affected by type 2 diabetes. *Diabetes Care* 2000; 23: 1857-1858.

11. Poitout V, Roberson R. Mini review: Secondary beta cell failure in type 2 diabetes - a convergence of glucotoxicity and lipotoxicity. *Endocrinology* 2002; 143: 339-342.

12. Ahima R, Flier J. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000; 11: 327-332.

13. Hawkins M, Gabriely I, Wozniac R et al. Glycemic control determines hepatic and peripheral glucose effectiveness in type 2 diabetic subjects. *Diabetes* 2002; 51: 2179-2189.

14. Dandona P, Alijada A, Mohanty P. The anti-inflammatory and potential anti-atherogenic effects of insulin: a new paradigm. *Diabetologia* 2002; 45: 924-930.

15. Alijada a, Ghanim H, Dandona P et al. Insulin inhibits NFkB andMCP-1 expression in human aortic and endothelial cells. *The J of Clinical Endocrinol and Metab* 2001; 86(1): 450-453.

16. Seshiah V, Balaji V. Early insulin therapy in type 2 diabetes. *Int J of Diabetes. Dev. Countries* 2003; 23: 90-93.

17. Porte D Jr. Banting Lecture 1990. Beta cells in type 2 diabetes mellitus. *Diabetes* 1991 ; 40 : 165-180.

18. Defronzo F. The Triumvirate: Beta cell, muscle and liver; a collusion responsible for NIDDM. *Diabetes* 1998. 347: 667-687.

19. Rachman J, Levy JC, Barrow BA et al. Changes in Amylin and Amylin like peptide concentration and beta cell function in response to sulfonylurea or insulin therapy in NIDDM. *Diabetes Care* 1998; 21: 810-816.

20. Bruttomesso D, Pianta A, Mari A et al. Restoration of early rise in plasma insulin levels improves glucose tolerance in type 2 diabetic patients. *Diabetes* 1999; 48: 99-105.

21. Iikova H, Benjamin G, Ayidin T et al. Induction of long term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 1997; 20: 1353-1356.

22. Priscilla A, Hollander P, Blonde L et al for the Exubera Phase III study Group. Efficacy and safety of Inhaled Insulin (Exubera) Compared with Subcutaneous Insulin Therapy in Patients with Type 2 Diabetes. *Diabetes Care* 2004; 27: 2356-2362.

23. Kjems LL, Holst JJ, Volund A et al. The influence of GLP-1 on glucose stimulated insulin secretion: effects on beta cell sensitivity in type 2 and non-diabetic subjects. *Diabetes* 2003; 52: 380-386.

24. Ratner RE, DeFronzo R, Pratley RE. Pros and Cons of GLP agonists versus DPP IV inhibitors. Current issues symposium. Program and abstracts of ADA, 67th Scientific sessions, June 22-26, 2007. Chicago, Illinois.