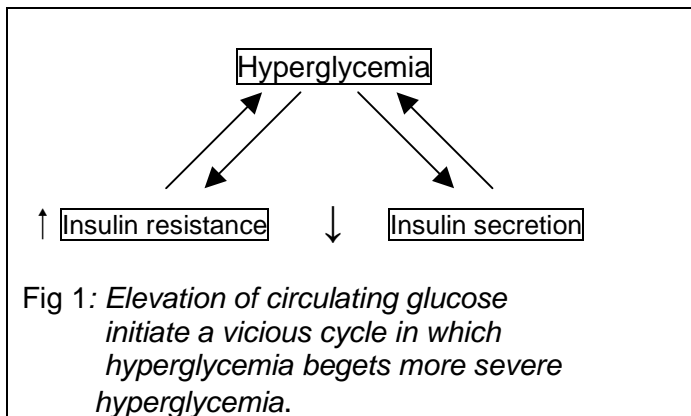


### *Symposium On Diabetes-3*

## **Insulin Therapy in Type 2 Diabetes Mellitus**

Type 2 diabetes is characterized by the combination of insulin resistance and deficient secretion of insulin. One of the most important hormones involved in nutrient homeostasis is insulin, a small polypeptide produced by the pancreatic beta cells. Insulin is crucial for the transport of glucose into the cell. The hormone binds to receptor sites on the cell membrane, which promotes movement of glucose – transport proteins from the interior to the surface of the cell. These proteins, in turn, bind glucose and carry it into the cell. The primary metabolic disease that occurs when the production or activity of insulin is inadequate is diabetes mellitus.

Hyperglycemia per se impairs the beta cell response to glucose and promotes insulin resistance (Fig 1). The exact mechanism remains uncertain; however, glucosamine product of glucose metabolism via the hexosamine pathway - has been implicated as a culprit. Reversal of glucotoxicity can disrupt the vicious cycle that perpetuates hyperglycemia, thereby facilitating therapeutic outcomes<sup>1</sup>.



Regardless of the cause, the disease is associated with a common hormonal defect, namely, insulin deficiency, which may be total, partial, or relative when viewed in the context of coexisting insulin resistance. Lack of insulin plays a primary role in the metabolic derangements linked to diabetes, and hyperglycemia in turn plays a key role in the complications of the disease.

Type 2 diabetes, accounts for over 95% of all diabetes in India. Typically it appears after the age of 40 years, has a high rate of genetic penetrance unrelated to HLA genes, and is associated with obesity. The clinical features of type 2 diabetes are much more insidious. The classic symptoms of diabetes may be mild (fatigue, weakness, dizziness, blurred vision, or other non-specific complaints may dominate the picture) or may be tolerated for many years before the patient seeks medical attention. Moreover, if the level of hyperglycemia is insufficient to produce symptoms, the disease may become evident only after complications develop.

The risk of developing type 2 diabetes increases with

- Age
- Obesity
- Lack of physical activity
- Family history of diabetes
- Genetic predisposition
- Women with prior gestational diabetes mellitus
- Individuals with hypertension or dyslipidemia

After having diagnosed and classified the glucose intolerance as that of type 2 diabetes, the clinician is left with a large problem- that of achieving good metabolic control to prevent and/or delay the complications of diabetes thereby improving the quality of life of patients under his care. Very few diseases call for a greater synergy between the patient and his clinician than does type 2 diabetes.

*Criteria for the diagnosis of diabetes mellitus<sup>2</sup>*

1. *Symptoms of diabetes plus casual plasma concentration  $\geq 200$ mg/ dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic or random symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.*  
Or
2. *FPG  $\geq 126$ mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hrs.*  
Or
3. *2-h PG  $\geq 200$  mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO<sup>2</sup> using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.*

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on the different day. The third measure (OGTT) is not recommended for routine clinical use.

At first the clinician is overwhelmed by the myths and conceptions that the patient has about his condition. Secondly, he has to orchestrate the interaction of the patient and the diabetes care team, an act that can only be compared with a tight rope walk with the ability of patient on one side and the demands of the team on the other.

The so called “*milder form of diabetes*”, or the earlier label of “*non-insulin-dependent*” add to the misery of the clinician while caring for the patient and emphasizing the need of good metabolic control while ensuring patient compliance to the therapeutic regimen.

The presence of hyperglycemia is a toxic state whether it occurs early or late in life and irrespective of its underlying cause. Results of the United Kingdom Prospective Diabetes Study (UKPDS) mandate that treatment of type 2 diabetes include aggressive efforts to lower blood glucose levels as close to normal as possible<sup>3</sup>.

### Therapeutic Objectives and Plan

- Achieve normal metabolic biochemical control
- Prevent microvascular and macrovascular complications

### Specific Goals of Therapy

- Eliminate symptoms
- Optimize metabolic parameters
- Assist the patient to achieve and maintain desirable body weight
- Improve cardiovascular risk factors, and
- Prevent and treat vascular complications

### Recommended treatment modalities include

- Dietary modification, (protein: 10-20%, fat saturated: < 10%; polyunsaturated: upto 10% of total caloric intake, carbohydrate intake: based on nutritional assessment and treatment goals)
- Regular physical activity, and
- Pharmacological intervention with either an oral hypoglycemic agent or insulin

<b>Glycemic control for people with diabetes<sup>4</sup></b>			
	<i>Normal</i>	<i>Goal</i>	<i>Additional action suggested</i>
<b>Whole blood values</b>			
<i>Average preprandial glucose (mg/dl)</i>	<100	80-120	<80/ > 140
<i>Average bedtime glucose (mg/dl)</i>	<110	100-140	<100/ > 160
<b>Plasma values</b>			
<i>Average preprandial glucose (mg/dl)</i>	<110	90-130	<90/ > 150
<i>Average bedtime glucose (mg/dl)</i>	<120	110-150	<110/ > 180
<i>Hb A<sub>1c</sub> (%)</i>	<6	<7	>8

The values shown in this table are by necessity generalized to the entire population with diabetes. Patients with combined disease, the very young and older adult, and others with unusual conditions or circumstances may warrant different treatment goals. These values are for non pregnant adults "Additional action suggested depends on individual patient circumstances. Such actions may include enhanced self-management education, co-management with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation of or increase in SMBG, or more frequent contact with the patient HbA is referenced to a nondiabetic of 4.0-6.0% (mean 5.0%, SD 0.5%). Measurement of capillary blood glucose values calibrated to plasma glucose.

### **Nutrition – Important Aspects**

- Patient education and behavior modification
- Individualization of the meal plan
- Maintaining near-normal blood glucose levels
- Normalizing serum lipid levels
- Attaining and maintaining a reasonable body weight
- Continuous follow-up

### **Exercise – Potential Benefits**

- Improvement in insulin sensitivity and improvement in glucose tolerance
- Promotion of weight loss and maintenance of desirable body weight when combined with restricted caloric intake
- Improvement of cardiovascular risk factors
- Potential reduction in dosage or need for pharmacological agents
- Enhancement of work capacity, and
- Enrichment of quality of life and improvement in sense of well - bring

Individualization and monitoring of an exercise programme is important and as such, should be undertaken following medical evaluation

### **Pharmacological Intervention – Based on**

- The level of blood glucose control desired
- The total clinical context of the patient's disease
- The patient's acceptance of the various therapeutic modalities
- The patient's age and weight
- The patient's ability for body self-care management
- The patient's level of diabetes education and motivation

The initial treatment of choice in patients with type 2 diabetes (Fig 2) is optimization of the meal plan and enhancement of physical activity. Diet and exercise therapy alone are not successful in controlling hyperglycemia in the majority of patients with type 2 diabetes. Less than 10% of patients will achieve an acceptable level of long – term glycemic control with nonpharmacological therapy alone. If progress toward glycemic goal is not apparent within a 3-month period after initiation of diet and exercise therapy, then the use of a pharmacological agent is appropriate. Diet therapy and a physical activity programme should always be reinforced. Some patients, however, require prompt pharmacological therapy with insulin (e.g., those with symptoms of hyperglycemia, those patients undergoing surgery, those with ketosis/HONK) at the time of diagnosis or first visit.



glucose uptake after meals. In type 2 diabetes, the primary goal is to restrain hepatic glucose overproduction.

### **Combination Therapy**

Presupper or bedtime administration of insulin to suppress the overnight hepatic glucose production to control fasting hyperglycemia and the addition of benzoic acid derivative – repaglinide (NovoNorm<sup>®</sup>) or alpha-glucosidase inhibitor to control postprandial hyperglycemia is an effective therapeutic option.

Patients most likely to benefit from combination therapy with metformin (OBIMET<sup>®</sup>) are those with marked insulin resistance required over 1 unit of insulin per kilogram body weight per day<sup>7</sup>.

### **Insulin**

- Reduces Fasting Hyperglycemia
- Reduces Hepatic Glucose Production
- Reduces Gluconeogenesis
- Improves Oxidative & Nonoxidative Glucose Disposal
- Induces Antiatherogenic changes in serum
- Lipid and Lipoprotein Profile
- Reduces unspecific glycosylation of proteins and Lipoproteins

If glycemic goals are not achieved with combination therapy, then treatment with insulin alone is indicated<sup>5</sup>. Patients with symptoms and marked hyperglycemia often benefit from the use of regular insulin (Actrapid<sup>®</sup> / Human Actrapid<sup>®</sup> / Actrapid<sup>®</sup> / HM Penfill<sup>®</sup>) along with an intermediate – acting insulin (Insulatard<sup>®</sup> / Human Monatard<sup>®</sup> / Human Insulatard<sup>®</sup> / Insulatard<sup>®</sup> HM Penfill<sup>®</sup>) when treatment is started. Otherwise, it is usually adequate to start an intermediate or long-acting insulin ( Insulatard<sup>®</sup> / Human Monatard<sup>®</sup> / Human Insulatard<sup>®</sup> / Insulatard<sup>®</sup> HM Penfill<sup>®</sup>) in the evening.

A reasonable starting dose is 0.2 to 0.3 units per kilogram of body weight per day<sup>7</sup>.

The patients daily glucose profile assists with further adjustments in insulin dosage. The dose may be increased by 2-4 units every 3-4 days if required. With evening NPH insulin (Insulatard / Human Insulatard<sup>®</sup> / Insulatard<sup>®</sup> HM Penfill<sup>®</sup>), a daytime rise in blood glucose indicates the need for adding morning NPH. When therapy is begun using NPH insulin in the morning, a rise in blood glucose overnight indicates the need for evening NPH insulin. Significant increases in blood glucose following meals demonstrates that adding regular insulin (Actrapid<sup>®</sup> / Human Actrapid<sup>®</sup> / Actrapid<sup>®</sup> HM penfill<sup>®</sup>) before the meals may be of benefit.

The use of premixed insulin may reduce patient errors in insulin dosing<sup>8</sup>. It is important to maintain the glycemic goals that have been attained by periodic assessment. Several important points about insulin therapy should be noted:

- Overnight hepatic glucose production, the main cause of fasting hyperglycemia
- Postprandial glycemic peak dependent on fasting glucose level.
- Overnight basal insulin supplementation, an optimal solution to reduce hyperglycemic peaks.
- When large doses of insulin are required, it is best to split the dose into two injections as intermediate-acting insulin (2/3<sup>rd</sup> daily insulin requirement in the morning and 1/3<sup>rd</sup> in the evening) and to use a combination of short – acting insulin plus intermediate – (Mixtard<sup>®</sup>/Human Mixtard<sup>®</sup> / Mixtard<sup>®</sup> HM Penfill<sup>®</sup>) or long – acting insulin.
- In the UKPDS, at the glycemic levels achieved, a small fraction of patients had a major episode of hypoglycemia regardless of the pharmacological therapy used<sup>3</sup>.
- It is important choose appropriate insulin delivery device (Novopen 3<sup>®</sup>/ NovoLet<sup>®</sup>) to improve compliance and thereby metabolic control, while ensuring dose accuracy and giving persons with diabetes more freedom in everyday life, and at the same time improving social acceptability of therapy and increasing patient confidence.

*References:*

1. Robert S. Sherwin. Diabetes Mellitus. Cecil Textbook of Medicine, 21st Ed., Orlando; W.B. Saunders: 2000.
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care, 23 (Suppl.1): S4-S19, 2000.
3. American Diabetes Association : Implications of the United Kingdom Prospective Diabetes Study (Position Statement). Diabetes Care 23(Suppl.1): S27-S31, 2000.
4. American Diabetes Association: Standards of Medical Care of Patients with Diabetes Mellitus (Position Statement). Diabetes Care 23 (Suppl.1): S32-S42, 2000.
5. American Diabetes Association : The Pharmacological Treatment of Hyperglycemia in NIDDM (Clinical Practice Recommendations) Diabetes Care 19 (Suppl.1): 1996.

6. Chow C-C, Tsang LWW, Sorensen JP, Cockram CS. Comparison of Insulin with or without Continuation of Oral Hypoglycemic Agents in the Treatment of Secondary Failure in NIDDM Patients. *Diabetes Care* 18; 5: 307-314, 1995.
7. Zimmerman BR New Trends in the Management of NIDDM Insulin Therapy : When and How ? The Association of Physicians of India. *Postgraduate Medicine*; 11(Suppl.): 1997.
8. Coscelli C, Calabrese G, Fedele D, Pisu E, et al. Use of Premixed Insulin Among the Elderly: Reduction of errors in patients preparation of mixtures. *Diabetes Care* 15; 1628-30: 1992.

### **Comments of Opinion Leaders:**

*"Timely initiation of insulin therapy halts the progress of diabetic complications. Insulin initiation improves the quality of life Positive reinforcement with patients about the benefit of insulin initiation is required to overcome patients reluctance to insulin".*

**- Dr. Shashank Joshi,  
Mumbai**

*"Patients not controlled by oral agents need an addition of insulin to attain normoglycemia. Good glycemic control has shown to significantly reduce the incidence of complications".*

**- Dr. Vijay Panikar,  
Mumbai**

*"In patients with oral hypoglycemic drug failure, insulin initiation improves glycemic control and thereby prevents late complications. In such a situation a dose of 8 to 10 units of intermediate acting insulin at night, in type 2 diabetic patients will provide better control without fear of hypoglycemia".*

**- Dr. Nalini Shah,  
Mumbai**

*"Type 2 diabetic patients are highly heterogeneous with many subgroups within it. Type 2 diabetics need not be 'Insulin Dependent' for life (like the IDDM) but can be insulin requiring for short periods or long periods and hence called insulin requiring NIDDM or IRDM. Timely treatment with insulin will correct glucotoxicity and can improve or restore insulin release in type 2 diabetics. Thus there are many advantages of insulin usage (for short periods) in early, mid or late type 2 diabetics".*

**- Dr. Sam G P Moses,  
Chennai**

