Role of Insulin in Type 2 Diabetes

Shashank R. Joshi

Introduction

Insulin was isolated and became available for clinical use in the early 1920s. It revolutionized the treatment of diabetes mellitus. Today, essentially all patients with type 1 diabetes and many patients with type 2 diabetes require insulin therapy. Although insulin has been available for more than 80 years, major advances have been made over the past 2 decades in the way insulin therapy is used in clinical practice. Much of the progress is a consequence of three factors, (a) The introduction of self-monitoring of blood glucose (SMBG) into routine practice, (b) A change in philosophy of diabetes management, such that patient self-management and flexibility in lifestyle have come to drive contemporary treatment approaches and (c) The development of insulin analogs that have time-action profiles aligned with physiological insulin secretion – both meal-related insulin secretion and basal insulin secretion.

The natural history of Type 2 Diabetes mellitus (DM) learnt from United Kingdom Prospective Diabetes Study (UKPDS) clearly shows the relentless progression of β-cell failure despite treatment. This obviously translates in the fact that even type 2 diabetic patients become insulin dependent sooner or later depending on the residual β-cell function. In addition they may need to be shifted to insulin temporarily under some situations. Moreover significant proportion of patients clinically diagnosed as type 2 DM may be Type 1a DM with relatively slow β-cell destruction, and would require insulin within months to years after diagnosis. Proper understanding of pharmacodynamics of insulin administration by the treating physician is utmost important. In addition proper patient education about injection technique is the responsibility of treating physician.

Insulin is the natural treatment of diabetes mellitus. It is the oldest, most potent, and natural treatment option, with unfortunately the highest risk perception. Insulin’s role in type 1, GDM and secondary diabetes is like a simple hormone deficiency, viz replacement agent. However, the optimal timing and indication of use of insulin in type 2 diabetes is a matter of considerable debate. Current evidence based thinking allows some practice guidelines in the optimal timing of insulin therapy.

Ideal Time to Use Insulin in Type 2 Diabetes

It is ideal to offer insulin therapy to every diabetic as an option, at diagnosis though most physicians offer it last. In fact there is emerging evidence that offering insulin therapy in prediabetic individuals with a vascular event may confer a metabolic advantage. The mega trial ORIGIN will provide answer to this issue. Ideally fasting hyperglycemia above 190 mg% should be offered insulin therapy at diagnosis to ensure that early insulin confers ‘beta cell rest’ and may have potential to remit diabetes. Most guidelines indicate insulin initiation in type 2 diabetes mellitus with fasting hyperglycemia above 250 mg%, the cut off of ketogenesis. In India, fasting blood glucose more than 190 mg%-250 mg%; post prandial blood glucose more than 250-300 mg% or glycosylated hemoglobin more than 10-12% must be offered insulin therapy. Right away after glucoxicity is settled and beta cell rest is ensured, the insulin can be appropriately downtitrated with the advent of PPARγ agents. In the next decade insulin may get another option to compete with.

The emerging global consensus (ADA, EASD, ICP - API, IDF) is the ideal time to add insulin in type 2 diabetes pharmacologically & pharmaceutically if 50% of a secretagogue (sulphonylurea) dose and sensitizer dose (metformin with or without glitazone) cannot get the glycosylated hemoglobin below 7% then is the ideal time to add insulin.

Dose of Insulin and Pharmacological Insulin Resistance

Insulin potency is measured in units. Originally, units were based on biological activity, but more recently, 1 mg insulin was defined to have 27.5 units of activity. In many countries, insulin preparations contain 100 units/ml and are known as U-100 insulin. For special circumstances,
highly concentrated U-500 short-acting (regular) insulin (500 units/ml) is available. In some parts of the world, insulin preparation contains 40 units/ml and are known as U-40 insulin. There is no upper due limit of insulin, though insulin requirement more than 200 iu/day is defined as ‘pharmacological’ insulin resistance. It is the most potent antidiabetic agent which can lower HbA1c more than 2% or greater.

**Extra-Glycemic Effects of Insulin in Type 2 Diabetes**

Similar to newer agents like glitazones insulin can improve endothelial function, cardiac function, lipid profile and can lower blood pressure. It can reduce PAI-1 hs CRP, and is anti-atherogenic. So the old myth that insulin is atherogenic is not valid and in fact reverse is true. Natural history of Type 2 Diabetes mellitus (DM) learnt from United Kingdom Prospective Diabetes Study (UKPDS) clearly shows the relentless progression of β – cell failure despite treatment. This obviously translates in the fact that even type 2 diabetic patients become insulin dependent sooner or later depending on the residual β – cell function. In addition they may need to be shifted to insulin temporarily under some situations. Moreover significant proportion of patients clinical diagnosed as type 2 DM may be Type 1a DM with relatively slow β – cell destruction, and would require insulin within months to years after diagnosis.

**Indications for Insulin Therapy in Type 2 Diabetes**

**Emergency situations**

Hyperosmolar non-ketotic coma is a well-known emergency in type 2 diabetic patients, especially in elderly. The precipitating factor in elderly age group is usually infection in urinary or respiratory tract. Rehydration with intravenous fluids, insulin and antibiotics with management of serum K+ is the mainstay of therapy, prognosis being poor with a mortality of around 50%. In intensive setup strict glycemic control with the use of insulin has demonstrated to reduce mortality. Patient may even present with severe hyperglycemia due to any sort of stress including acute severe illnesses. Though there is no cutoff for initiation of early insulin treatment may be beneficial.

**Myocardial infarction / vascular events / angioplasty / cardiac bypass surgery**

Ischaemic heart disease (IHD) is 2-4 times more common in diabetic patients. Diabetic patients presenting with myocardial infarction (MI) have increased mortality. DIGAMI study has demonstrated 30% reduction in mortality by insulin treatment, though DIGAMI - 2 study was equivocal. It was later shown that strict glycemic control is more important irrespective of mode of achieving it, insulin should be the treatment of choice in these patients till they are stable.

**Perioperative insulinization**

Diabetic patients undergoing surgery are at increased risk of metabolic complications and infections. All diabetic patients going for major surgery and all patients with uncontrolled hyperglycemia should be shifted to insulin. Various protocols have been suggested for administering insulin, glucose and K+. Insulin therapy during surgery needs hospital policies which are now well known.

**Renal and Liver failure**

Patients developing diabetic nephropathy have relentless decline in glomerular filtration rate culminating in end stage renal disease. In patients with renal failure all oral hypoglycemic agents are contraindicated. Patients with early renal insufficiency develop hypoglycemia due to renal elimination of insulin. These patients usually require smaller doses of insulin. For the same reason all patients with liver dysfunction should be shifted to insulin.

**Secondary OHA Failure**

By natural history of diabetes, patients develop secondary OHA failure at the rate of 5-8% per year and 80% of the patients require insulin by 10 years and all by 20 years. In such patients oral agents should be continued at optimal doses if not contraindicated otherwise. Initially addition of bed time dose of NPH insulin may restore glycemic control.

**TB and Diabetes (Patient on Anti TB Treatment)**

Rifampicin is known to enhance metabolism of sulphonylureas, worsening the glycemic control. In addition insulin has beneficial effects by virtue of its anabolic effects. Patients who are well controlled on OHA along with anti TB agents, may not be shifted to insulin.

**Insulin Strategies for Type 2 Diabetes**

Recommended blood glucose targets for patients with type 2 diabetes are summarized in Table 1. When patients have been placed on a stable diet and activity program, they can be divided by degree of severity into four groups – mild, moderate, severe, and very severe – based on their level of fasting glycemia and their ability to restore postprandial glycemia to basal levels (as a measure of intactness of prandial insulin secretion).

**Table 1 : Representative Plasma Blood Glucose Levels Suitable for Patients with Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Normal</th>
<th>Goal</th>
<th>Additional Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average preprandial glucose (mg/dl)</td>
<td>&lt;100</td>
<td>80-120</td>
<td>&lt;80 &gt;140</td>
</tr>
<tr>
<td>Average bedtime glucose (mg/dl)</td>
<td>&lt;110</td>
<td>100-140</td>
<td>&lt;100 &gt;160</td>
</tr>
<tr>
<td>Plasma values Average preprandial glucose (mg/dl)</td>
<td>&lt;110</td>
<td>90-130</td>
<td>&lt;90 &gt;150</td>
</tr>
<tr>
<td>Average bedtime glucose (mg/dl)</td>
<td>&lt;120</td>
<td>110-150</td>
<td>&lt;110 &gt;180</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

**Mild Type 2 Diabetes**

Insulin therapy is rarely used for patients with mild type 2 diabetes, i.e. individuals with fasting plasma glucose less than 126 mg/dl. However a vascular event or surgery or emergency may predate use of insulin. Lifestyle modification with or without insulin sensitizers especially metformin is the preferred choice for this group.
Moderate Type 2 Diabetes

For patients with moderate type 2 diabetes, i.e. individuals with fasting plasma glucose 126-200 mg/dl, if insulin therapy is used, basal insulin therapy alone is often sufficient, with endogenous insulin secretion (perhaps facilitated by oral agents) being adequate to control meal-related prandial glucose excursions. Basal insulinemia may be initiated by long-acting (or intermediate-acting) insulin at bedtime. Required doses are generally in the range of 0.3-0.4 units/kg/day, but may be initiated by 8 - 10 units at bedtime and increasing the dose every week based on prevailing fasting glucose. Basal insulin therapy serves to supplement the patient’s basal insulin secretion and provides sufficient insulin to overcome the prevailing insulin resistance. The most popular insulin initiation strategy in type 2 diabetes is “BIDS” protocol viz bedtime insulin (NPH in the past and glargine / determir) with daytime sulphonylurea (glimiperide). The rationale to add bedtime basal insulin was to treat the overnight hepatic glucose production.

Severe Type 2 Diabetes

For patients with severe type 2 diabetes, i.e. individuals with fasting plasma glucose more than 200 mg/dl, around-the-clock insulinization is usually necessary (bedtime intermediate-acting insulin cannot be used). Most patients in this category require the addition of short-acting insulin to attain adequate glucose control. Doses required are generally in the range of 0.5-1.2 units/kg/day. However, large doses, even more than 1.5 units/kg/day, may be required at least initially to overcome prevailing insulin resistance. Such high-dose therapy may be necessary only to attain control, with subsequent control maintained on lower doses, on a basal insulin program, or even with oral hypoglycemic agents. Often, insulin therapy is continued at doses in the range of 0.3-1.0 units/kg/day. Premixed insulin may be used.

Very Severe Type 2 Diabetes

The last category is patients with very severe type 2 diabetes, i.e. individuals with nonintact endogenous insulin response to meals, such that postprandial glycemia is not resolved to basal levels within 5 h of meal consumption. In such individuals, fasting plasma glucose is usually quite elevated as well, i.e. more than 250-300 mg/dl, but this category may include individuals with lesser degrees of fasting hyperglycemia. The insulin deficiency is so profound that, initially, these patients may be difficult to distinguish from patients with type 1 diabetes patients, they are best treated like type 1 diabetes patients initially.

In all patients with type 2 diabetes, pathophysiological defects improve as glycemic control is attained and maintained. This facilitates control and may permit patients initially treated with insulin to be maintained with oral hypoglycemic agents or even on a diet and activity program alone.

Most patients with type 2 diabetes can be controlled with insulin if adequate doses are given and if the patient follows an appropriate meal and exercise program. The latter facilitates insulin action. Failure to follow a diet may countermand the effects of insulin and lead to a vicious cycle of progressively increasing insulin doses with failure to control glycemia.

Transient Insulin Therapy

One important use of insulin is as temporary therapy. This therapy is used (a) to initially attain glycemic control in patients with severe type 2 diabetes, (b) to overcome glucose toxicity and (c) to re-regulate decompensated patients.

Insulin Therapy in Type 2 Diabetes

In individualised motivated, compliant and well educated patient who can accurately administer insulin and self monitored glucose intensive insulin regimens are most efficient and effective. The caveats in type 2 diabetes are elderly as well as cases who care long standing with hypoglycemic unawareness or severe neuropathy. The patient and their family members need education on hypoglycaemia recognition, treatment and prevention. There is no one dose or one regimen which can be used in all patients, in fact for each patient individualised doses and titration needs to be done. Most intensive regimens used basal - bolus strategy or split - mix strategy and rarely need insulin pump.

References