Insulin in Diabetes

Diabetes not only causes destruction of the body as a whole but also leads to a lot of psychological stress. The patients need to do a lot of self-care, which remains a vital and essential factor in maintaining the glycemic control. Hence, a thorough understanding is expected from the physician side to explain the intricacies to the patient.

Type 1 and Type 2 Diabetes Mellitus

The main difference between the type 1 and type 2 diabetes mellitus is that type 1 diabetes mellitus has a complete deficiency of required amount of insulin and type 2 diabetes mellitus is caused by insulin resistance (insulin deficiency can also occur in varying amount, but is not the primary cause). Type 1 diabetes is an autoimmune disease that leads to a destruction of the beta cells of the pancreas.

In type 1 diabetes mellitus insulin is given as replacement therapy while in the case of type 2 diabetes insulin is given for the control of hyperglycemia and the insulin is added when initial treatment with non-pharmacological like exercise, diet control, weight reduction and oral medication like metformin are not able to control the glucose level.
Insulin Development

In the past, insulin was extracted from animals for the use of the treatment in humans. This resulted in the development of antibodies against the injected insulin in some of the patients, leading to complications.

This was resolved by the introduction of biosynthetic human insulin, which is manufactured by using the recombinant DNA technology. There are two categories of recombinant insulin.

One is the rapid-acting insulin, which is intended to be used after a meal. It has an effect around the 15 minutes after giving the injection. The second is long-acting insulin which has an effect lasting for around 24 hours (basal insulin). A combination of the two is usually used for the treatment of diabetes.

Insulin is administered subcutaneously or parenterally (it is destroyed by gastric acid). Long- or intermediate-acting insulin constitutes the basal insulin and it is normally given as one to two injections per day. The short- or rapidly-acting insulin constitutes the prandial insulin and is given three or more times a day.

Mechanism of Action

Insulin facilitates glucose intake into the cell by increasing potassium intake (a mechanism which is an asset for the treatment of hyperkalemia). The main mechanism of degradation of insulin is receptor-mediated endocytosis followed by degradation by insulin degrading enzymes.

<table>
<thead>
<tr>
<th>Liver</th>
<th>Skeletal muscle</th>
<th>Adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases glycogen synthesis</td>
<td>Increase glycogen synthesis</td>
<td>Increases triglyceride storage</td>
</tr>
<tr>
<td>Decreases protein catabolism</td>
<td>Increases protein synthesis</td>
<td>Decreases protein catabolism</td>
</tr>
<tr>
<td>GLUT 2 into cell membranes</td>
<td>GLUT 4 into cell membranes</td>
<td>GLUT 4 into cell membranes</td>
</tr>
<tr>
<td>Increased synthesis:</td>
<td></td>
<td>Increased synthesis/activity</td>
</tr>
<tr>
<td>• Pyruvate Kinase</td>
<td></td>
<td>• Lipoprotein Lipase</td>
</tr>
<tr>
<td>• Phosphofructokinase</td>
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<tr>
<td>• Glucokinase</td>
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</table>

Insulin also decreases the glucose level by increasing the synthesis of glycogen (the storage form of glucose), decreasing the formation of new glucose (gluconeogenesis), and channeling the glucose into lipid synthesis pathway.
Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

Types of Insulin

<table>
<thead>
<tr>
<th>Types of insulin</th>
<th>Begins to work after injection</th>
<th>Peak at work after injection</th>
<th>Continues to work after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting insulin</td>
<td>Insulin glulisine, Insulin lispro, Insulin aspart</td>
<td>15 minutes</td>
<td>-</td>
</tr>
<tr>
<td>Regular or short-acting insulin</td>
<td>Regular insulin</td>
<td>30 minutes</td>
<td>2 to 3 hours</td>
</tr>
<tr>
<td>Intermediate-acting insulin</td>
<td>NPH (Neutral Protamine Hagedorn)</td>
<td>2 to 4 hours</td>
<td>4 to 12 hours</td>
</tr>
<tr>
<td>Long-acting insulin</td>
<td>Insulin detemir and insulin glargine</td>
<td>several hours</td>
<td>-</td>
</tr>
</tbody>
</table>

Indications

Type 1 diabetes mellitus

Insulin is given as a replacement therapy for the patients.

Type 2 diabetes mellitus

Metformin is the first drug for the treatment of type 2 diabetes. If metformin only therapy is not effective, another oral anti-diabetic drug or insulin can be added. Insulin is preferred in patients with glycated hemoglobin greater than 9.5%, persistent random glucose level greater than 300 mg/dl, presence of ketones in urine and fasting blood glucose greater than 215 mg/dl.
Other variants of diabetes mellitus
In case of gestational diabetes mellitus, insulin is not the preferred therapy but if it is needed, Insulin detemir is the one usually used.

Insulin Treatment in Patients of Type 1 Diabetes Mellitus
The aim in the treatment of patients with type 1 diabetes mellitus is to maintain the glycated hemoglobin level (HbA1c) at a value of 7% or lower.

The insulin therapy is to provide a complete physiological alternative (replacement therapy). Treatment consists of administration of basal insulin (long-acting or intermediate insulin or continuous administration of subcutaneous insulin) 1 to 2 times a day and regular or short-acting insulin pre-meal.

The amount of the pre-meal bolus is to be determined by a number of factors such as the quality and composition of the food to be taken in the meal, the amount of activity expected after taking the food, and the glucose level before the meal.

Hypoglycemia can occur frequently, so stringent glucose monitoring is required – at least 6 times a day (self-monitoring of blood glucose (SMBG)).

In addition to this, education, proper nutrition, and activity (30 minutes of aerobic activity) form an important aspect of the management. It is required to modify the insulin administration based on the exercise undertaken.

Multiple dose insulin (MDI) regimens
There are different types of multiple-dose insulin (MDI) regimen which are available and the benefit of the one regimen over the other cannot be fully substantiated. The modest glycemic benefit, which is seen with the regimens containing insulin analog, is not backed up by the corresponding benefit in the cardiovascular outcome (trials are lacking).

Continuous subcutaneous insulin infusion
As the name describes, the insulin is administered in a continuous manner and only the short or regular insulin is used. But the disadvantage is that it is not economical and there is a sudden chance for complication due to machine malfunction.

The choice between the continuous and the injection treatment is mainly based on the patient preference. The efficacy and the hypoglycemic episodes are the same with both the regimens. In one of the trial, it was demonstrated that when a patient was given the choice of both, more than half chose continuous subcutaneous therapy.
The factors like the variability in the intra-day insulin requirement and the inherent antagonising hormones in the body need to be taken care of when giving the insulin through the pump.

The types of the insulin pump which are available in the market are as follows:

- Sensor-augmented insulin pump
- Automated closed-loop insulin pump
- Bihormonal closed-loop system
- Insulin-only closed-loop system

### Insulin Treatment in Patients of Type 2 Diabetes Mellitus

For those patients who are not responding to oral hypoglycemic drugs, insulin can be added as a therapy. Metformin is the drug which is commonly used in combination with insulin.

When the patients are first started on insulin, it is commonly recommended to start on basal insulin, rather than prandial insulin. The idea is that the occurrence of hypoglycemic episodes is relatively less with the basal insulin.

### Disadvantages of Insulin

Weight gain and hypoglycemic attack are concerns with the use of insulin in the treatment of type 2 diabetes. Insulin also has the risk of causing hypokalemia and causing lipodystrophy at the injection site. Another rare side effect is the risk of immunogenicity (allergic anaphylactic reaction).

### Insulin as a Diagnostic Tool

Very rarely, insulin can be used for the diagnosis of pituitary function problems. Insulin tolerance tests can be used to assess the integrity of the hypothalamic-pituitary-adrenal axis.
References


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Notes