

# Insulin in Diabetes

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**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.**



## Types 1 and 2 Diabetes Mellitus

There are 2 main types of diabetes mellitus: type 1 and type 2. In type 1, patients have a **complete deficiency of the required amount of insulin**; type 2 is caused by **insulin resistance** (insulin deficiency can also occur in varying amounts, but it is not the primary cause). Type 1 diabetes is an autoimmune disease that leads to **the destruction of the beta cells of the pancreas**.

In type 1 diabetes mellitus, insulin is given as **replacement therapy**, while in type 2, insulin is given for the **control of hyperglycemia** and is added when initial treatment with non-pharmacological treatments such as exercise, diet control, weight reduction, and oral medication (i.e. **metformin**) are not able to control a patient's glucose level.

# Insulin Development

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

This barrier was resolved through the introduction of **biosynthetic human insulin**, which is manufactured by using recombinant DNA technology.

There are 2 categories of recombinant insulin. The first category is **rapid-acting insulin**, which is intended to be administered after a meal. It takes effect approximately 15 minutes after the injection. The second category is **long-acting insulin**, which lasts for around 24 hours (**basal insulin**). A combination of the 2 types of insulin is usually used to treat diabetes mellitus.

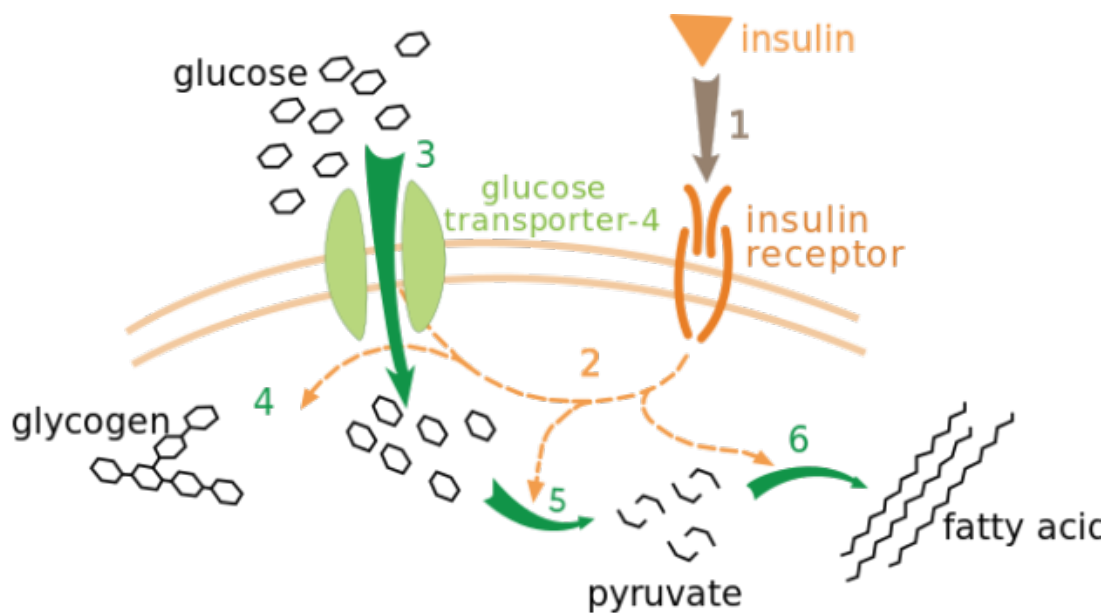
Insulin is administered **subcutaneously or parenterally**, as it is destroyed by gastric acid. Long- or intermediate-acting insulin constitutes basal insulin and is normally administered through 1 to 2 injections per day. Short- or rapidly acting insulin constitutes prandial insulin and is administered 3 or more times a day.

## Mechanism of Action

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

Liver	Skeletal Muscle	Adipose Tissue
Increases glycogen synthesis	Increases glycogen synthesis	Increases triglyceride storage
Decreases protein catabolism	Increases protein synthesis	Decreases protein catabolism
Stimulates incorporation of glucose transporter (GLUT) 2 into cell membranes	Stimulates incorporation of GLUT 4 into cell membranes	Stimulates incorporation of GLUT 4 into cell membranes
Increases synthesis of: <ul style="list-style-type: none"><li>• Pyruvate kinase</li><li>• Phosphofructokinase</li><li>• Glucokinase</li></ul>		Increases synthesis/activity of: <ul style="list-style-type: none"><li>• Lipoprotein lipase</li></ul>

Insulin also decreases glucose levels by increasing the synthesis of glycogen (the storage form of glucose), decreasing the formation of new glucose (**gluconeogenesis**), and channeling the glucose into a lipid synthesis pathway (see image below).



**Image:** 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). By: XcepticZP. License: [Public Domain](#)

## Types of Insulin

Types of insulin	Examples/Brand names	Time Until It Begins to Work After Injection	Peak Time After injection	Duration
Rapid-acting	Insulin glulisine, insulin lispro, insulin aspart	15 minutes	-	2-4 hours
Regular or short-acting	Regular insulin	30 minutes	2-3 hours	3-6 hours
Intermediate-acting	Neutral protamine hagedorn	2-4 hours	4-12 hours	12-18 hours
Long-acting	Insulin detemir and insulin glargine	Several hours	-	Over a 24-hour period

## Indications

### Type 1

Insulin is given as replacement therapy.

### Type 2

**Metformin** is the drug of choice 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 > 9.5%, persistent random glucose level > 300 mg/dL, the presence of ketones in urine, and fasting blood glucose > 215 mg/dL.

## Other Variants

In patients with gestational diabetes mellitus, insulin is not the preferred therapy; however, if necessary, insulin detemir can be administered.

## Insulin Treatment in Patients with Type 1 Diabetes Mellitus

The aim when treating patients with type 1 diabetes mellitus is to maintain the **glycated hemoglobin level (HbA1c)** at a value of 7% or lower.

Insulin therapy provides a complete **physiological alternative (replacement therapy)**. Treatment consists of the 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 before meals**.

The amount of the **pre-meal bolus** is determined by a number of factors, including the quality and composition of the food to be eaten, the amount of activity likely to be engaged in after eating, and the patient's glucose level before the meal.

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

In addition, education, proper nutrition, and activity (30 minutes of aerobic activity per day) are an important part of symptom management. In fact, insulin administration can be modified based on results achieved from exercise.

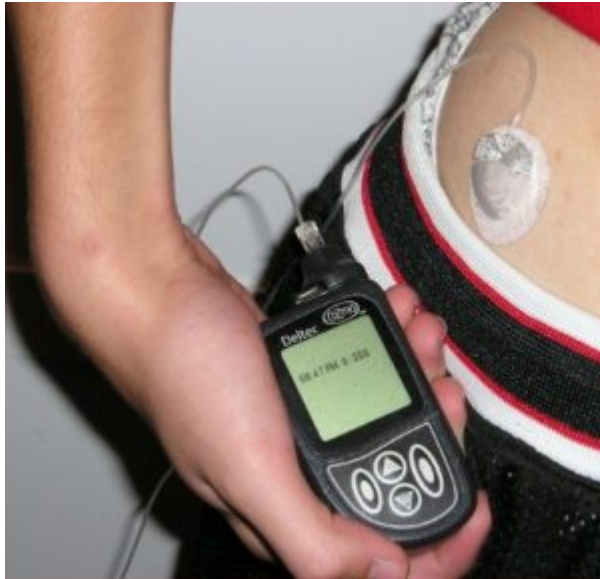
## Multiple-Dose Insulin (MDI) Regimens

Different types of MDI regimens are available, and the benefits of 1 regimen over another are unclear. The **modest glycemetic benefit** that is seen with regimens that include insulin analog is not backed up by a corresponding benefit in the **cardiovascular outcome**, as clinical trials are lacking.

## Continuous Subcutaneous Insulin Infusion

As its name denotes, in this mode of treatment, insulin is administered in a continuous manner and **only short-acting or regular insulin is used**. The disadvantage of using this mode is that it is not economical, and, as well, complications due to insulin pumps can occur.

The decision to use either continuous or injection treatment is mainly based on **patient preference**, as the efficacy and hypoglycemic episodes are the same. In 1 trial, it was demonstrated that when a patient was given a choice, more than half chose continuous subcutaneous therapy.



**Image:** Insulin pump with an infusion set. By: Mbradford at English Wikipedial; transferred from en.wikipedia to Commons.  
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Factors such as the **variability in intra-day insulin requirements** and **inherent antagonizing hormones** in the body need to be taken into account when administering insulin through the pump (see image below).

The types of insulin pumps currently available are as follows:

- Sensor-augmented
- Automated closed-loop
- Bihormonal closed-loop
- Insulin-only closed-loop

## Insulin Treatment in Patients with Type 2 Diabetes Mellitus

For patients who do not respond to oral hypoglycemic drugs, insulin can be added as a therapy. **Metformin** is the drug most commonly used in combination with insulin. When patients are first started on insulin, it is recommended that they begin with **basal insulin**, rather than **prandial insulin**, as hypoglycemic episodes are less likely with basal insulin.

### Disadvantages

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

### Insulin as a Diagnostic Tool

Very rarely, insulin can be used to diagnose [pituitary function](#) problems, as insulin tolerance tests can help assess the integrity of the [hypothalamic-pituitary-adrenal axis](#).

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