WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 5, 229-251. Review Article ISSN 2277–7105

INSULIN THERAPIES IN DIABETES

Utkarsh Patel*, Vidhi Yadav[1], Shivani Shukla[2] and Dr. Alok Kumar Shukla[3]

[*1]Student, Babu Sunder Singh College of Pharmacy, Raebareli Road, Nigohan, Lucknow.

[2]Lecturer, Babu Sunder Singh College of Pharmacy, Raebareli Road, Nigohan, Lucknow.

[3]Director, Babu Sunder Singh College of Pharmacy, Raebareli Road, Nigohan, Lucknow.

Article Received on
08 January 2024,

Revised on 29 Jan. 2024,
Accepted on 18 Feb. 2024

DOI: 10.20959/wjpr20245-31418

***Corresponding Author**
Utkarsh Patel
Student, Babu Sunder Singh College of Pharmacy, Raebareli Road, Nigohan, Lucknow.

ABSTRACT

To study the insulin-related issues that are commonly seen in most of the peoples of the world due to imbalances in their blood glucose levels. And also, to study the therapies used in the treatment of diseases that arise due to insulin disbalance like diabetes mellitus type 1 and 2. Various delivery systems of insulin have been studied and their effects over time. This review represents the pharmacology, pharmacokinetics, and various molecular aspects which may be helpful shortly based on available published data. This review opens various doors or acts as a backbone for various types of research shortly popular worldwide.

KEYWORDS: Various delivery systems of insulin have been studied and their effects over time.

1.1 INTRODUCTION

The peptide hormone known as insulin, which is produced by the beta cells of the islets of the pancreas, is produced by the human insulin (INS) gene. The word "island" is derived from the Latin word insula. It appears to be the body's primary anabolic hormone. It facilitates the digestion of glucose from the blood by the liver, adipose tissue, and skeletal muscle cells. This, in turn, controls the metabolism of proteins, fats, and carbohydrates. Within these tissues, the glucose that is absorbed is either transformed via lipogenesis into fatty acids or in the case of the liver, into both glycogen and fats. High blood insulin concentrations severely limit the liver's ability to synthesize and release glucose. Furthermore, insulin circulation affects the synthesis of proteins in various tissues. Diabetes is a chronic illness that affects how your body uses food as fuel over a longer amount of energy.[1]

The majority of the food you eat is converted by your body into glucose, or sugar, which is then distributed throughout your bloodstream. Your pancreas releases insulin in a reaction to an increase in blood sugar. Insulin allows blood sugar to enter your body's cells and be used as a source of energy.

Diabetes results in either insufficient insulin production or inefficient insulin use by the body. When you have too little insulin or when cells develop a resistance to the hormone, your sugar level rises. That might ultimately end in major health issues like kidney problems, coronary artery disease, and blindness.[2]

Diabetes presently has no known cure, but after a nutritious diet, getting regular exercise, and managing the condition are all highly beneficial. Additional behaviors you can do to assist.

- As directed, take your medication.
- Receive assistance and education on diabetes self-management.
- Schedule and honor medical appointments.

1.2 History

An important turning point in the history of medicine was the discovery of insulin, especially in the context of diabetes management. Diabetes is a long-term medical condition that was Charles Best, a medical student, and professor of physiology J.J.R. once frequently fatal.

The story starts in the early 1900s when there were few treatment options and diabetes was a poorly understood illness. Before insulin, the primary method of treating diabetes was to follow stringent dietary guidelines, which frequently proved insufficient in cases of extreme diabetes.

A group of researchers at the University of Toronto made a significant discovery in 1921, which led to a breakthrough. The group comprised Canadian physician Sir Frederick Banting, Charles Best, a medical student, and professor of physiology J.J.R. Macleod.[4]

- To isolate the pancreatic secretion thought to contain the anti-diabetic substance, Banting and Best developed an experimental strategy. Through canine experiments, they were able to prove that the dogs developed diabetes when the pancreas was severed. Subsequently, they extracted the pancreatic extract and injected it into the diabetic dogs, renaming it "isletin" (later renamed insulin) to effectively normalize their blood sugar levels.

- After joining the group, Collip helped to refine the insulin extract, increasing its effectiveness and lowering adverse effects. The group's work was crucial in creating a more streamlined and practical form of insulin for use in treating humans. The first successful insulin trials on humans were conducted in 1922. Leonard Thompson, a young diabetic boy 14 years old, was in critical condition and was the first patient to receive insulin. His life was saved by the dramatic and instantaneous effect of the insulin injections.[5]
- The discovery of insulin changed the course of diabetes treatment, turning the fatal illness into a condition that can be managed. Despite some disagreement over the team's credit allocation, for their roles in the discovery, Macleod and Banting received the Nobel Prize in Medicine or Physiology in 1923.[4]
- Since then, insulin has helped millions of diabetics worldwide by saving their lives. For those with diabetes, the discovery of insulin has improved their quality of life and given them hope, making it one of the greatest medical discoveries ever.

1.3 Importance of insulin in glucose homeostasis

Insulin plays a crucial role in glucose homeostasis, which refers to the maintenance of a stable pancreas secretes the hormone insulin, which is vital for controlling the metabolism of glucose. The following are some significant facets of insulin's role in maintaining glucose homeostasis.

1. Glucose Uptake by Cells

1. After a meal or other event that causes blood glucose levels to rise, Insulin gets released into the bloodstream from the pancreas.
2. Insulin helps cells, particularly muscles and adipose (fat) cells, absorb glucose. It facilitates the bloodstream's transportation of glucose into these cells.[6]

2. Stimulation of Glycogenesis

1. Insulin promotes glycogenesis, which is the conversion of glucose into glycogen. When blood glucose levels fall, the muscles and liver store glycogen, which is a readily available energy source.

3. Inhibition of Gluconeogenesis

1. The liver uses gluconeogenesis, which is inhibited by insulin, to produce glucose from non-carbohydrate sources. This aids in preventing the overproduction and release of glucose into the blood.

4. Suppression of Lipolysis

1. The release of fatty acids from stored fat is suppressed by insulin. This process helps prevent excess fatty acids from entering the bloodstream and encourages the body to use glucose as fuel by blocking the breakdown of fat.[7]

5. Enhancement of Protein Synthesis

1. Insulin promotes the synthesis of proteins in cells, helping in the maintenance and growth of tissues. This is important for overall cellular function and repair.

6. Regulation of blood glucose levels

1 Insulin helps control blood glucose levels by promoting the ingestion of glucose cells and encouraging its storage as glycogen. This keeps the level of glucose in the blood from rising too high and gives cells a steady supply of energy.[8]

7. Neurological Function

1. Insulin aids in blood glucose regulation by promoting glucose uptake into cells and its storage as glycogen. This keeps blood glucose levels from rising too high and gives cells a steady supply of energy.

8. Role in Energy Balance

1. A crucial component of the complex equilibrium between energy intake and expenditure is insulin. It aids in controlling how glucose is used as fuel and how much extra nutrition is stored.

9. Prevention of Hyperglycaemia

1. Insufficient insulin or insulin resistance can lead to hyperglycemia, a condition characterized by elevated blood glucose levels. Chronic hyperglycemia can contribute to various health issues, including diabetes and its complications.

In summary, insulin is essential for maintaining glucose homeostasis by promoting glucose uptake by cells, regulating glycogen storage, inhibiting gluconeogenesis and lipolysis, and supporting overall metabolic balance. Dysfunction in insulin production or action can lead to imbalances in blood glucose levels, contributing to metabolic disorders like diabetes.

1.4 Insulin structure and biosynthesis

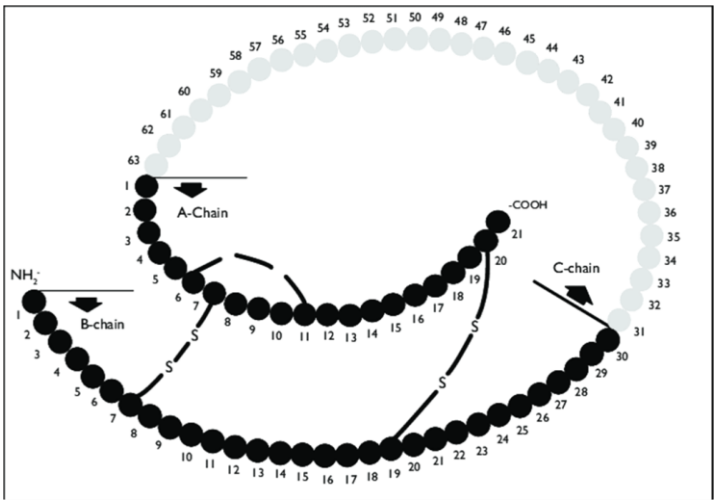

Fig 2.

Made up of two amino acid chains, A and B, that are associated with disulfide bonds, your body is a peptide hormone. The molecular structure of insulin can be described in terms of its amino acid sequence and the arrangement of its disulfide bonds. The primary structure of human insulin consists of 51 amino acids.[9]

21 amino acids are contained by chain A, and 30 amino acids are contained by chain B. The two chains are connected by two disulfide bonds, one between the A chain and B chain at positions A7 and B7, and the other at positions A20 and B19.

Here is a simplified representation of the primary structure of human insulin.
A chain: Glycine-Serine-Cysteine-Threonine-Proline-Cysteine-Serine-Valine-Cysteine-Threonine-Glycine B chain: Isoleucine-Alanine-Leucine-Threonine-Proline-Valine Cysteine-Threonine-Lysine-Leucine-Cysteine-Valine-Threonine.

The disulfide bonds are formed between the cysteine residues at specific positions in the A and B chains. The three-dimensional structure of insulin is important for its biological activity, and the arrangement of the disulfide bonds contributes to the stability and function of the molecule.

It's worth noting that insulin can exist in different forms, including a monomeric form and a hexameric form when stored in the pancreas or pharmaceutical formulations. The hexameric form is more stable and has a longer duration of action, but it needs to undergo structural changes to become active when released into the bloodstream.

1.5 Biosynthesis and processing of insulin pancreatic beta cells

One hormone that is essential for controlling Insulin binds to glucose, also known as blood sugar, in the body. The production and release of insulin are handled by the beta cells found in the pancreas. There are multiple steps involved in the production and breakdown of insulin in pancreatic beta cells, including transcription, translation, presentation, and post-translational modifications.

Synopsis of the procedure[10]

1. Transcription

1. The process starts with the beta cell nucleus' the transcription of the insulin gene (INS). Preproinsulin, the insulin precursor, has coding regions found in the insulin gene.

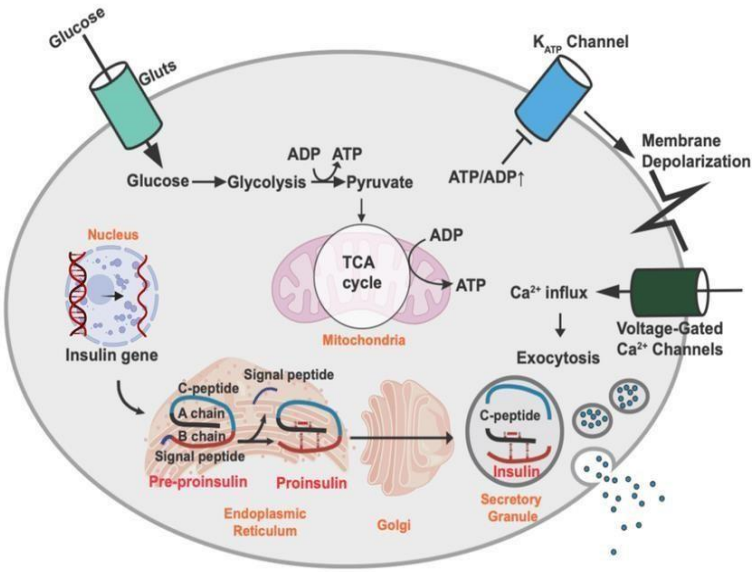

Fig 3.

1. Translation

1. The mRNA transcript is then transported from the nucleus to the cytoplasm, where it serves as a template for protein synthesis.
2. The mRNA is translated into pre-proinsulin, a precursor protein, by ribosomes located in the cytoplasm.

2. Signal Peptide Cleavage

1. A signal peptide found in pre-proinsulin directs it to the endoplasmic reticulum (ER). Proinsulin is created as a result of the signal peptide being broken off.

3. Formation of Disulfide Bonds

1. The endoplasmic reticulum folds proinsulin, stabilizing its structure through disulfide bonds between particular cysteine residues.

4. Transport to Golgi Apparatus

1. Proinsulin is then transported from the endoplasmic reticulum to the Golgi apparatus.

5. Further Processing in the Golgi

1. Proinsulin experiences additional post-translational changes in the Golgi apparatus, such as the cleavage of the connecting peptide (C-peptide). The mature insulin and C-peptide are produced as a result of this cleavage.

6. Packaging into Secretory Granules

1. Inside the beta cells are secretory granules containing mature insulin. These granules contain various enzymes and proteins that facilitate the regulated release of insulin.

7. Secretion of Insulin

1. Pancreatic beta cells are stimulated to release insulin in reaction to higher blood glucose levels. This release is tightly regulated and occurs in response to signals such as elevated blood glucose.

8. Cleavage of C-peptide

1. Upon secretion, insulin and C-peptide are initially released in equimolar amounts. In the bloodstream, C-peptide is gradually cleaved from insulin. Therefore, the measurement of C-peptide levels can be used as an indirect indicator of insulin secretion.

The entire process is finely tuned to ensure that insulin is released in response to changes in blood levels of glucose, helping to maintain glucose homeostasis in the body.

Dysregulation of insulin synthesis or secretion can lead to disorders such as diabetes mellitus. Insulin receptors play a crucial role in signal transduction, particularly in the context of glucose homeostasis and metabolism. Here's a brief overview of the role of insulin receptors in signal transduction.[11]

1. Insulin and Glucose Homeostasis

1. The pancreatic beta cells release the insulin hormone in response to high blood glucose levels, which can occur after a meal.
2. Insulin's main role is to help and make it easier for cells, especially muscle and adipose (fat) cells, to absorb glucose and to stop the liver from producing glucose.
3. Insulin helps maintain blood glucose levels within a narrow range, preventing hyperglycemia (high blood sugar) and its associated complications.

2. Insulin Receptor Structure

1. The insulin receptor is a transmembrane protein that spans the cell membrane.
2. It has two alpha and two beta subunits linked with disulfide bonds.
3. The extracellular portion of the receptor contains the insulin-binding sites, while the intracellular portion has tyrosine kinase activity.

3. Insulin Binding and Activation

1. When insulin binds to its receptor on the cell surface, it induces a change in the receptor.
2. These changes activate the intrinsic tyrosine kinase activity of the receptor.

4. Tyrosine Kinase Activity

1. The insulin receptor phosphorylates tyrosine and activates residues on itself (autophosphorylation) and on intracellular substrate proteins.
2. Different signaling molecules dock at these phosphorylated tyrosine residues.

1. Insulin Signalling Cascade

3. Activation of the insulin receptor initiates a cascade of intracellular signaling events.
4. Phosphorylated tyrosine residues on the receptor recruit and activate Insulin receptor substrate (IRS) proteins are a few instances of downstream signaling proteins.

5. PI3K-Akt Pathway

1. One of the major signaling pathways activated by insulin is the PI3K-Akt pathway.
2. Insulin activates phosphatidylinositol 3-kinase (PI3K), which causes phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to be produced.
3. PIP3 triggers the activation of protein kinase Akt, which in turn controls the uptake of glucose, the synthesis of glycogen, and the synthesis of proteins.

6. MAPK Pathway

1. Insulin also activates the mitogen-activated protein kinase (MAPK) pathway. initiates the pathway known as mitogen-activated protein kinase, or MAPK.
2. This pathway is involved in cell growth, differentiation, and gene expression.

7. Cellular Responses

1. The combined effect of insulin signaling is increased glucose uptake by cells, decreased glucose production by the liver, and modulation of various cellular processes to promote energy storage and growth.

In summary, insulin receptors play a pivotal role in signal transduction by transmitting the signal initiated by insulin binding into the cell, ultimately regulating glucose homeostasis and various cellular processes crucial for energy balance and growth. Dysregulation of insulin signaling is associated with conditions such as Diabetes and insulin resistance mellitus.

1.6 Role of insulin receptors in signal transduction

Insulin receptors play a role in signal transduction, particularly in the context of glucose homeostasis and metabolism. Here's a brief overview of the role of insulin receptors in signal transduction.[12]

Insulin and Glucose Homeostasis

The pancreatic beta cells release the hormone insulin in reaction to high blood glucose, which can occur after a meal. Insulin's principal roles include promoting muscle and adipose (fat) cell uptake of glucose and impeding the liver's ability to produce glucose.

By keeping blood sugar levels within a specific range, insulin helps avoid hyperglycemia (high blood sugar) and the problems that come with it.

Insulin Receptor Structure

A transmembrane protein that passes the cell membrane is the insulin receptor. It is made up of two beta and two alpha subunits linked by disulfide bonds. The insulin-binding sites are located in the extracellular region of the receptor, whereas tyrosine kinase activity is located in the intracellular portion.

Insulin Binding and Activation

The conformation of the insulin receptor is altered when it binds to its cell surface receptor. This conformational shift activates the intrinsic tyrosine kinase activity of the receptor.

Expression of Tyrosine Kinase

The activated insulin receptor phosphorylates tyrosine residues on itself (autophosphorylation) and on intracellular substrate proteins. These phosphorylated tyrosine residues serve as docking sites for various signaling molecules.

Insulin Signalling Cascade

A series of intracellular signaling events are triggered by the activation of the insulin receptor. Insulin receptor substrate (IRS) proteins and other downstream signaling proteins are attracted to and activated by phosphorylated tyrosine residues on the receptor.

PI3K-Akt Pathway

The PI3K-Akt pathway is one of the main signaling pathways that insulin activates. Phospholipid inositol (3,4,5)-trisphosphate (PIP3) is produced when insulin activates phosphatidylinositol 3-kinase (PI3K). PIP3 triggers the activation of protein kinase Akt, which in turn controls multiple cellular functions such as the uptake of glucose, the synthesis of glycogen, and the synthesis of proteins.

MAPK Pathway

Additionally, the mitogen-activated protein kinase (MAPK) pathway is activated by insulin. This pathway is involved in cell growth, differentiation, and gene expression.

Cellular Responses

The combined effect of insulin signaling is increased glucose uptake by cells, decreased glucose production by the liver, and modulation of various cellular processes to promote energy storage and growth.

In summary, insulin receptors play a pivotal role in signal transduction by transmitting the signal initiated by insulin binding into the cell, ultimately regulating glucose homeostasis and various cellular processes crucial for energy balance and growth. Dysregulation of insulin signaling is associated with conditions such as insulin resistance and diabetes mellitus.

1.7 Insulin Physiology

The pancreatic beta cells secrete the hormone insulin, which is responsible for regulating the body's glucose metabolism. Below is a summary of insulin physiology.[13]

Synthesis and Release

Insulin is synthesized as proinsulin in the beta cells of the pancreatic islets of Langerhans. Proinsulin is then cleaved into insulin and C-peptide. While insulin is released into the bloodstream, C-peptide can be measured as a marker of insulin secretion.

Stimuli for Insulin Release

High Blood Glucose Levels: An increased blood glucose level is the main factor that triggers the release of insulin. After a meal, the pancreas releases insulin to help cells absorb glucose when blood glucose levels rise.

Amino Acids: Protein-rich meals can also stimulate insulin release, as amino acids trigger insulin secretion.

Gastrointestinal Hormones: Hormones released from the gastrointestinal tract, such as incretins (e.g., GLP-1), can enhance insulin secretion.

Insulin's Actions

Insulin Facilitates Cell Uptake of Glucose: Insulin promotes cell uptake of glucose, especially in muscle and adipose (fat) tissues. By increasing the number of glucose transporters on the cell membrane, it enhances the transport of glucose into these cells.

Glycogen Synthesis

Insulin promotes the synthesis of glycogen in the liver and muscles. Glycogen is a storage form of glucose.

Protein Synthesis

Insulin stimulates protein synthesis in various tissues.

Inhibition of Glucose Production

The process by which the liver makes glucose from non-carbohydrate sources is called gluconeogenesis, and insulin inhibits it.

Lipogenesis

Insulin promotes the synthesis of lipids (fats) in adipose tissue by stimulating the conversion of glucose to triglycerides.

Insulin inhibits lipolysis, the process of breaking down stored fat, which lessens the amount of fatty acids released into the blood. Regulation of Insulin Activity.

Insulin Sensitivity

The effectiveness of insulin in promoting glucose uptake varies among individuals. Insulin sensitivity refers to how responsive cells are to the effects of insulin.

Insulin Resistance

In conditions like obesity and type 2 diabetes, cells may become resistant to the actions of insulin, leading to elevated blood glucose levels.

Insulin Degradation

Insulin is broken down and cleared from the bloodstream by the liver and kidneys.

Metabolic disorders like diabetes mellitus can result from disruptions in the production of insulin or its actions. Because of the autoimmune destruction of beta cells, type 1 diabetes is characterized by an insulin deficiency; in type 2 diabetes, however, insulin resistance and impaired insulin secretion are frequently combined.

1.8 Insulin and diabetes

Diabetes is a disease triggered by elevated blood glucose, which is additionally referred to as blood sugar. Your body uses glucose as its main source of energy. Although it can also be produced by the body, glucose can be obtained from food.

The pancreas secretes the hormone insulin, which facilitates the uptake of glucose by your cells for use as fuel. When you have diabetes, your body either doesn't produce enough insulin or doesn't use it correctly. Glucose keeps in your blood after that and doesn't enter your cells.

Diabetes raises the risk of kidney, nerve, heart, and eye damage. Diabetes and certain types of cancer are connected. If you take steps to prevent or manage your diabetes, you may be able to lower your risk of developing health issues related to diabetes.

The three most common kinds of diabetes are type 1, type 2, and gestational diabetes.

Type 1 diabetes

If you have type 1 diabetes, your body generates very little or no insulin. The cells in your pancreas that generate insulin are targeted by your immune system and eliminated. Although it may show up at any age, children and young adults are usually diagnosed with type 1 diabetes. People with type 1 diabetes need to take insulin daily to survive.

Type 2 diabetes

The cells in your body are unable to utilize insulin as effectively if you're suffering from type 2 diabetes. While a certain amount of insulin may be produced by the pancreas, not enough is produced to maintain blood glucose levels within normal ranges. The most prevalent type of the disease is type 2 diabetes. In addition to risk factors like being overweight or obese, getting a family history of type 2 diabetes raises your risk of developing the condition. Type 2 diabetes can develop in early childhood or even at any age. Type 2 diabetes can be delayed or even prevented by recognizing the risk factors and laying nutritious eating habits into execution, such as maintaining or reducing weight.

Gestational Diabetes

One kind of diabetes that appears during pregnancy is called gestational diabetes. After the baby is born, this kind of diabetes usually disappears. On the other hand, having gestational diabetes increases your risk of developing type 2 diabetes later in life. Type 2 diabetes is occasionally confused with pregnancy-related diabetes.

Prediabetes

Patients with prediabetes have higher blood glucose levels than healthy individuals, but not to the point where type 2 diabetes can be diagnosed. If you have prediabetes, you have a higher chance of developing type 2 diabetes later in life. In addition, your risk of heart disease is higher than that of individuals with normal glucose levels.

Other types of diabetes

One gene mutation is the cause of monogenic diabetes, a less common form of the disease. Diabetes may also result from pancreatic surgery, pancreatitis, or other conditions that damage the pancreas. Cystic fibrosis is one such condition.

1.9 Insulin Resistance

Your muscles, fat, and liver cells' improper insulin response causes insulin resistance, also known as impaired insulin sensitivity. Your pancreas produces the hormone insulin, which regulates blood glucose (sugar) levels and is essential for life. Insulin resistance can be either temporary or persistent, and it can be treated under certain conditions.

Under normal circumstances, insulin normally carries out the following functions.
Your body's main energy source is glucose, sometimes known as sugar, which it gets from the food you eat.

Insulin is generated by your pancreas in response to glucose entering your bloodstream. Muscle, fat, and liver cells can either use or store blood glucose for later use when it is absorbed quicker because of insulin.

Blood glucose levels fall and glucose enters your cells, which stops the pancreas from producing insulin.

It may be difficult for your muscle, fat, and liver cells to properly absorb or store glucose from your blood due to a wide range of factors affecting how they respond to insulin. That's insulin resistance. Then, your pancreas produces more insulin in an attempt to counteract your rising blood glucose levels. This is referred to as hyperinsulinemia.

When glucose enters your cells and blood glucose levels fall, the pancreas stops producing insulin.

For a variety of reasons, your muscle, fat, and liver cells may not respond to insulin as they should, which makes it difficult for them to properly absorb or store glucose from your blood. This is known as insulin resistance. Then, in an attempt to counteract your blood glucose levels, your pancreas produces more insulin. This is known as hyperinsulinemia.

As long as your pancreas can produce enough insulin to counteract your cells' weak response to insulin, your blood sugar levels will stay within a healthy range. Overly resistant cells to insulin result in hyperglycemia or elevated blood sugar. Over time, this can result in prediabetes and Type 2 diabetes.

Insulin resistance is linked to multiple medical conditions apart from Type 2 diabetes. These conditions include.

- Polycystic Ovary Syndrome (PCOS).
- Metabolic syndrome.
- Cardiovascular disease.
- Non- Obesity.
- alcoholic fatty liver disease.

1.10 Insulin delivery system

A variety of tools, including a syringe and vial, an insulin pen, and continuous subcutaneous insulin infusion (CSII), can be used to deliver insulin subcutaneously. This article reviews and summarizes the benefits and drawbacks of each subcutaneous insulin delivery method in Table 1.

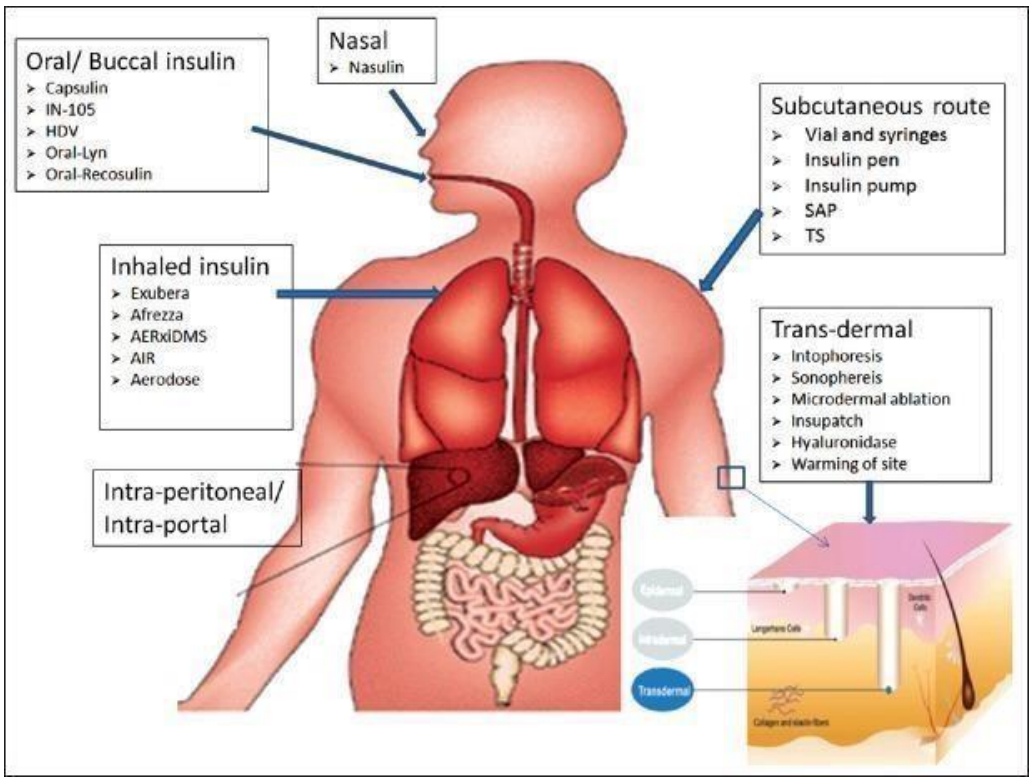

Figure 4: Routes of drug administration.

Table 1: Insulin delivery methods advantages and disadvantages.

Methods	Advantages	Disadvantages	Remarks
Insulin delivery through subcutaneous route			
Vial and syringe	↓Expensive versus pen and CSII	↑Pain versus pens Psychosocial issues Inconvenience to carrying it ↓Accurate versus pens ↓Patient friendly	Most frequently used method
Pen device	Convenient ↓Pain versus syringes More accurate, precise versus syringes Easier to use	More expensive versus syringes Can't mix two insulins	No superiority of pen devices versus syringes for glycemic control
CSII (Accu-Chek® Spirit, OneTouch Ping MiniMed Paradigm, DANA Diabecare IIS, OmniPod, Nipro Amigo, T-slim)	Continuous delivery of insulin Better glycemic control ↑Patient compliance and acceptance	↑Cost ↑Risk of DKA if pump fails injection site infection	Successful CSII needs patients education and requires motivation
SAP (any of the above pumps+Dexcom G4, Minimed, FreeStyle Navigator)	Same as CSII+better glycemic control ↓Hypoglycemia	Same as CSII CGM accuracy	Better glycemic control requires contentious CGM use
TS (Paradigm Revel 2.0 insulin pump and Enlite glucose sensor)	All the advantage of SAP+reduce hypoglycemia by 30% versus CSII	Same as CSII and SAP Hypoglycemia algorithms not predictive	Approved recently by FDA Phase 4 survey underway
Intra-peritoneal (MIP 2007)	Direct insulin delivery to the portal vein More physiological	Invasive ↑Cost Infection, portal vein thrombosis risk↑	Long-term data not available
Inhaled (Exubera, Technosphere, AERx, insulin Diabetes Management System)	Noninvasive ↑Patient compliance Rapid onset of action (10-15 min) Better PPBG control	↓Bioavailability Inhalational devices issues ↓Lung function Transient cough	Exubera withdrawn from the market Technoshere under FDA review
Oral (Capsulin, ORMD-0801, IN-105)	↑Portal insulin concentration Noninvasive Patient friendly	GI degradation of insulin ↓Bioavailability	Result of phase 3 trial awaited-IN-105
Buccal (Oral-Lyn, Recosulin)	Same as oral+bypass GI degradation	↓Bioavailability	Phase 3 trial result awaited
Nasal (Nasulin)	Same as oral and buccal insulin+no interference with pulmonary functions	↓Bioavailability (15-25%) Local irritation Nasal irritation	Phase 2 and 3 clinical trials awaited
Transdermal (Microneedles, iontophoresis, electrophoresis, sonophoresis microdermalabration)	Needle free	Skin irritation, blister, pain and redness	No long-term trials Safety not established

↑: High, ↓: Less,+: Plus, DKA: Diabetic ketoacidosis, FDA: Food and Drug Administration, CSII: Continuous subcutaneous insulin infusion, TS: Threshold suspend insulin pump, SAP: Sensor-augmented pump therapy, GI: Gastro-intestinal, CGM: Continuous glucose monitor, PPBG: Postprandial blood glucose

Syringe and vial

The Greek word "syrinx," which means "tube," is where the word "syringe" originated. The first syringes were developed in 1853. The Fergusson syringe, which helped to create the modern syringe, was among the first syringes. The first parenteral route for drug delivery was intravenous, which was first recorded in the late 17th century using syringes and needles.[14] The subcutaneous route was developed in the early 19th century. In 1924, two years after the discovery of insulin, Becton, Dickinson, and Company (BD) created a syringe specifically designed for injecting the drug. The first syringes were reusable, constructed of glass or metal, and needed to be boiled after each use to sterilize them. Disposable syringes were created to lower the frequency of infections linked to needle use. The first glass disposable syringes were mass-produced by BD in 1954 and were known as the BD Hypak. Over the past 50 years, a lot of changes have been made to contemporary insulin syringes and needles. Even with all of these improvements, many patients are still unable to inject insulin three or four times a day due to needle fear. Recently, the I-port Advance® injection port was created.

It is the first device that eliminates the need for multiple injections without necessitating skin punctures in between doses by combining an inserter and an injection port into a single unit. The patient having needle phobia can use this device and can control the glycaemic index in the blood.[15]

Insulin Pen

The use of vial and syringe insulin injections is restricted due to the inconvenience and error in preparing the insulin dose. These issues led to the development of insulin pens. In 1985, NovoNordisk created the first insulin pen. After this, many pharmaceutical companies improved their products over the next thirty years.[16] The more modern insulin pens are safer, more precise, and have reusable designs with audible clicks for each dosage to reduce the chance of human error. The built-in recording of the time and date of the last 16 injections is another innovation in the pen device, the Huma Pen® MemoirTM. NoVo Pen Echo®, which combines dosing in half-unit increments with an easy-to-use, straightforward interface, was recently designed to give parents and kids more confidence. Because of this, insulin pens are more expensive than vials and syringes but also more precise, practical, painless, and patient-friendly.[17] Because of problems with reimbursement and factors about patients and physicians, Insulin pen usage differs significantly between countries; in Europe, it is higher (approximately 80%) and in the USA, it is lower (about 15%).[17][18][19]

Recently developed pen needles (31-32 G × 4-5 mm) are shorter and thinner, causing less pain and requiring less time and thumb force to inject insulin, thus improving patient satisfaction.

The latest smart pens are made to help people with diabetes who require insulin by providing them with instructions on how much insulin to take.[18] They do this by using built-in calculators, memory features that help them remember how much to take at what time, and Bluetooth technology to automatically transfer the insulin dose to a mobile logbook.[20][21][22]

Continuous subcutaneous insulin infusion

Increased physiologic insulin delivery has long been desired. In a healthy body, the pancreatic beta cells continuously secrete a small amount of insulin to lower the amount of glucose produced by the liver. When food is consumed, the pancreas secretes a larger amount of insulin to maintain euglycemia.[23] While hemoglobin A1c (A1c) goals can be successfully met with multiple daily injections (MDI) therapy, this method differs from the insulin

secreted by pancreatic beta cells. As a result, it's linked to high glycaemic variability (hypo- and hyperglycemia).

Kadish created the first portable insulin pump in 1963, but its functionality was restricted by its size and technical problems. Since then, changes have been made to improve its effectiveness and patient comfort. In the USA, the first commercial insulin pump was unveiled in 1979. CSII therapy was used in almost 40% of the intensive arm of the DCCT trial.[24][25][26] The newer generation of insulin pumps has smaller dimensions and clever features like alarms and dose calculators integrated right into the device, making them more patient-friendly.

Studies have shown that CSII is superior to MDI therapy in terms of lowering insulin dosages (~14%), reducing hypoglycemia and glycaemic variability, improving patient satisfaction and quality of life, and reaching glycaemic goals (~0.5% A1c reduction).[27][28][29] The higher cost of CSII therapy in comparison to MDI, the potential for subcutaneous infections, the inconvenience of being hooked up to a device, and the potential for higher risk of diabetic ketoacidosis are some of its drawbacks. It is crucial to educate patients before beginning CSII therapy to prevent these side effects.[30][31]

Sensor-augmented pump therapy

Combining the use of a pump and continuous glucose monitor (CGM) for diabetes management is now possible due to advancements in CGM technology. The most recent iterations of CGMs have been demonstrated to enhance glycaemic control in T1DM patients and to be more precise and compact Sensor-augmented pump (SAP) therapy involves adjusting insulin pump delivery based on CGM readings. Using SAP reduces A1c in T1DM patients by 0.7–0.8% in comparison to baseline or MDI therapy. To adjust insulin pump delivery based on CGM glucose readings, SAP requires patient participation OR THRESHOLD PUMP. As a result, SAP is vulnerable to human error. Moreover, waking up is required for SAP therapy to treat nocturnal hypoglycemia.

Sensor-augmented pump with low sugar

For patients with type 1 diabetes, hypoglycemia is the most feared acute insulin therapy complication. More than half of hypoglycemia episodes happen at night, and while they are uncommon, nocturnal hypoglycemia accounts for 6% of deaths in younger T1DM patients. Furthermore, nocturnal hypoglycemia cannot be eliminated by the MDI, CSII, or SAP. To

prevent nocturnal hypoglycemia, the first step in creating an artificial pancreas (closed-loop system) is to stop delivering insulin once CGM glucose reaches a low threshold (typically 70 or 60 mg/dl).[32][33][34]

The threshold suspends (TS) system will stop delivering insulin for up to two hours if a patient disregards a low glucose alert.[38] This function will not prevent hypoglycemia; rather, it is intended to lessen its severity and duration.[35] Insulin suspension for two hours does not increase the risk of developing ketone bodies or cause severe hyperglycemia or diabetic ketoacidosis. In clinical trials, TS decreased the duration of severe hypoglycemia and the severity of nocturnal hypoglycemia by 30–40% without changing A1c values. The US Food and Drug Administration (FDA) has recently approved the TS system, which was previously approved in 2009 in other nations.[36][37][39]

1.11 Challenges in insulin therapy

Challenges in insulin therapies are in.

- **Precision and Personalization:** Achieving precise and personalized insulin therapy is challenging. Individuals vary in their response to insulin, and factors such as age, weight, diet, and physical activity need to be considered. Advancements in precision medicine and personalized treatment plans may help address this challenge.
- **Hypoglycaemia and Hyperglycaemia Management:** Striking the right balance between avoiding hyperglycemia (high blood pressure) and hypoglycemia (low blood sugar level) is a continuous challenge. Newer insulin formulations and delivery systems aim to mimic the body's natural insulin release more closely to reduce these risks.
- **Patient Adherence and Education:** Ensuring patient adherence to insulin therapy regimens and providing adequate education on insulin administration, glucose monitoring, and lifestyle management are crucial. Barriers to adherence include fear of injections, lack of understanding, and the complexity of treatment plans.
- **Cost and Access:** The cost of insulin and related supplies can be a barrier to treatment for some individuals, leading to issues of affordability and accessibility. Efforts are being made to address these concerns, including the development of more affordable insulin options and increased awareness about available assistance programs.
- **Technological Advances and Integration**: Continuous glucose monitoring (CGM) and insulin pump technologies have advanced, providing more options for patients. However, integrating these technologies into seamless and user-friendly systems remains a

challenge. Interoperability and compatibility between different devices need improvement.

- **Insulin Resistance:** People having diabetes develop resistance as a result of their cells not responding to insulin. Managing insulin resistance is a challenge, and research is ongoing to understand the underlying mechanisms and develop targeted therapies.
- **Autoimmune Response to Insulin:** In some cases, the body's immune system may develop antibodies against exogenous insulin, potentially affecting its efficacy. Finding ways to mitigate or prevent this autoimmune response is an area of ongoing research.
- **Long-acting and Ultra-Rapid-Acting Insulin Formulations:** While there have been advancements in long-acting and ultra-rapid-acting insulin formulations, achieving the ideal balance between duration of action, onset, and peak is an ongoing challenge.

It's important to note that the landscape of diabetes management, including insulin therapy, is dynamic, and researchers and healthcare professionals are continuously working to address these challenges through innovative approaches and technologies. Always consult with healthcare professionals for the most up-to-date information on diabetes management and insulin therapy.

REFERENCE

1. Voet D, Voet JG (2011). *Biochemistry* (4th ed.). New York: Wiley.
2. Stryer L (1995). *Biochemistry* (Fourth ed.). New York: W.H. Freeman and Company, pp. 773–74. ISBN 0-7167-2009-4.
3. National diabetes statistics report, 2022. Centers for Disease Control and Prevention. Updated January 18, 2022. Accessed August 4, 2022.
4. Rosenfeld L. Insulin: discovery and controversy. *Clin Chem*, 2002; 48: 2270–88. [PubMed] [Google Scholar]
5. Krishnamurthy K (2002). Pioneers in scientific discoveries. Mittal Publications. p. 266. ISBN 978-81-7099-844-0. Retrieved 26 July 2011.
6. "Lehninger Principles of Biochemistry" by David L. Nelson and Michael M. Cox.
7. "Endocrinology: An Integrated Approach" by Stephen Nussey and Saffron A. Whitehead
8. "Williams Textbook of Endocrinology" by Shlomo Melmed, Kenneth S. Polonsky, P. Reed Larsen, and Henry M. Kronenberg.
9. Fu Z, Gilbert ER, Liu D (January 2013). "Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes". Current Diabetes Reviews, **9**(1): 25–53.

10. Steiner, D. F., & Oyer, P. E. (1967). The biosynthesis of insulin and a probable precursor of insulin by a human islet cell adenoma. Proceedings of the National Academy of Sciences, 57(2): 473-480.
11. Duckworth, W. C., & Kitabchi, A. E. (1974). Insulin secretion from the human pancreas: comparison of insulin, proinsulin, and C-peptide secretory rates from the isolated, perfused human pancreas. Diabetes, 23(3): 198-204.
12. "Lehninger Principles of Biochemistry" by Nelson and Cox or "Molecular Biology of the Cell" by Alberts et al.
13. American Diabetes Association. (2020). "Standards of Medical Care in Diabetes—2020." Diabetes Care, 43(Supplement 1): S1-S212.
14. Milestones BD. [Last accessed on 2013 Sep 16]. Available from: http://www.bd.com/aboutbd/history/
15. Fry A. Insulin delivery device technology 2012: Where are we after 90 years? J Diabetes Sci Technol, 2012; 6: 947–53. [PMC free article] [PubMed] [Google Scholar]
16. Selam JL. Evolution of diabetes insulin delivery devices. J Diabetes Sci Technol, 2010; 4: 505–13. [PMC free article] [PubMed] [Google Scholar]
17. Novo Nordisk Blue sheet. Quarterly perspective on diabetes and chronic diseases. 2010. [Last accessed on 2014 Sep 13]. Available from: http://www.press.novonordisk-us.com/bluesheet-issue2/downloads/NovoNordisk_Bluesheet_Newsletter.pdf.
18. Penfornis A, Personeni E, Borot S. Evolution of devices in diabetes management. Diabetes Technol Ther, 2011; 13(Suppl 1): S93–102. [PubMed] [Google Scholar]
19. Ignaut DA, Venekamp WJ. HumaPen Memoir: A novel insulin-injecting pen with a dose-memory feature. Expert Rev Med Devices, 2007; 4: 793–802. [PubMed] [Google Scholar]
20. Reynolds C, Antal Z. Analysis of the NovoPen Echo for the delivery of insulin: A comparison of usability, functionality, and preference among pediatric subjects and their parents, and health care professionals. J Diabetes Sci Technol, 2010; 4: 1476–8. [PMC free article] [PubMed] [Google Scholar]
21. Pfützner A, Bailey T, Campos C, Kahn D, Ambers E, Niemeyer M, et al. Accuracy and preference assessment of prefilled insulin pen versus vial and syringe with diabetes patients, caregivers, and healthcare professionals. Curr Med Res Opin, 2013; 29: 475–81. [PubMed] [Google Scholar]

22. Xue L, Mikkelsen KH. Dose accuracy of a durable insulin pen with memory function, before and after simulated lifetime use and under stress conditions. Expert Opin Drug Deliv, 2013; 10: 301–6. [PubMed] [Google Scholar]
23. Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, Beebe C, et al. Quantitative study of insulin secretion and clearance in normal and obese subjects. J Clin Invest, 1988; 81: 435–41. [PMC free article] [PubMed] [Google Scholar]
24. Kadish AH. A servomechanism for blood sugar control. Biomed Sci Instrum. 1963; 1: 171–6. [PubMed] [Google Scholar]
25. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. Continuous subcutaneous insulin infusion therapy for children and adolescents: An option for routine diabetes care. Pediatrics, 2001; 107: 351–6. [PubMed] [Google Scholar]
26. Skyler JS, Ponder S, Kruger DF, Matheson D, Parkin CG. Is there a place for insulin pump therapy in your practice? Clin Diabetes, 2007; 25: 50–6. [Google Scholar]
27. Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: The impact of baseline A1c. Diabetes Care, 2004; 27: 2590–6. [PubMed] [Google Scholar]
28. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: Meta-analysis of randomized controlled trials. BMJ, 2002; 324: 705. [PMC free article] [PubMed] [Google Scholar]
29. Müller-Godeffroy E, Treichel S, Wagner VM. German Working Group for Paediatric Pump Therapy. Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus — a large-scale multicentre pilot study. Diabet Med, 2009; 26: 493–501. [PubMed] [Google Scholar]
30. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: A meta-analysis. Diabetes Care, 2003; 26: 1079–87. [PubMed] [Google Scholar]
31. Moser EG, Morris AA, Garg SK. Emerging diabetes therapies and technologies. Diabetes Res Clin Pract, 2012; 97: 16–26. [PubMed] [Google Scholar]
32. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care, 1999; 22(Suppl 2): B40–2. [PubMed] [Google Scholar]
33. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. Diabetes Care, 2012; 35: 1814–6. [PMC free article] [PubMed] [Google Scholar]
34. Brazg RL, Bailey TS, Garg S, Buckingham BA, Slover RH, Klonoff DC, et al. The ASPIRE study: Design and methods of an in-clinic crossover trial on the efficacy of

automatic insulin pump suspension in exercise-induced hypoglycemia. J Diabetes Sci Technol. 2011; 5: 1466–71. [PMC free article] [PubMed] [Google Scholar]

35. Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, et al. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: The in-clinic ASPIRE study. Diabetes Technol Ther, 2012; 14: 205–9. [PubMed] [Google Scholar]
36. Beck RW, Raghinaru D, Wadwa RP, Chase HP, Maahs DM, Buckingham BA, et al. Frequency of morning ketosis after overnight insulin suspension using an automated nocturnal predictive low glucose suspend system. Diabetes Care, 2014; 37: 1224–9. [PMC free article] [PubMed] [Google Scholar]
37. Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, et al. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. Diabetes Technol Ther, 2011; 13: 1129–34. [PubMed] [Google Scholar]
38. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med, 2013; 369: 224–32. [PubMed] [Google Scholar]
39. Finn T. Medtronic Unveils FDA-Approved “Artificial Pancreas”-T1 Diabetes Patients Need to Take Note. Healthcare Matters Healthcare Matters. 2013. Oct 1, [Last accessed on 2013 Oct 27]. Available from: http: //www.hcmatters.com/2013/10/medtronic-unveils-fda-approvedartificial-pancreas-t1-diabetes-patients-need-to-take-note/