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Review Article

Subcutaneous Insulin - Various Delivery Devices

Authors
Dr P.Sharmila Nirojini[1], Aiswaria M S[2], Abisha R S[3], Abburi. Lalitha Nandini[4], Abitha Aravindakshan[5]
[1]M.Pharm, PhD, HOD, Department of pharmacy practice, Swamy Vivekananda College of pharmacy
[2,3,4,5]Pharm.D Intern, Swamy Vivekananda College of Pharmacy

Abstract
Diabetes causes abnormalities in carbohydrate, fat, and protein metabolism due to insulin's ineffective action on target tissues. Insulin is a peptide hormone produced by the beta-cells of the pancreatic islets of Langerhans and is responsible for facilitating cellular glucose uptake and regulating carbohydrate, lipid, and protein metabolism. Insulin is injected into the fat layer subcutaneously, or beneath the skin. In this form of injection, a small needle is used to inject insulin into the fatty layer between the skin and the muscle. In comparison to a typical vial or syringe, the insulin pen was proved to be significantly easier to use and less unpleasant. Some characteristics of an insulin pen may make it more suitable for certain patients, and physicians must be aware of these requirements.
Keywords: *Diabetes mellitus, Subcutaneous Insulin, Insulin pen, Insulin pump, Syringes, Insulin delivery.*

Diabetic Mellitus

Diabetes is a chronic, metabolic disorder characterized by high levels of blood glucose (or blood sugar), which may lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves.[1] Hyperglycaemia is a symptom of diabetes, which is caused by a defect in insulin secretion, insulin action, or both. Diabetes can be developed by a variety of pathogenic processes. These can range from autoimmune destruction of beta-pancreatic cells, which causes insulin deficiency, to abnormalities that cause insulin resistance.

Diabetes causes abnormalities in carbohydrate, fat, and protein metabolism due to insulin's ineffective action on target tissues. Inadequate insulin secretion and/or decreased tissue responses to insulin cause insulin deficiency at one or more points along the complex hormone action pathways. Insulin secretion and insulin action defects often coexist in the same patient, making it difficult to determine which abnormality is the primary cause of hyperglycaemia, if either.[2]

Types of Diabetes Mellitus

Diabetes is categorized into several types:

• **Juvenile diabetes** is an autoimmune disorder. In the pancreas, where insulin is produced, the immune system attacks and destroys the β-cells. It's unclear what's causing this attack. Approximately 10% of diabetic patient have this type of diabetes.

• **Type 2 diabetes mellitus** is caused by the body's resistance to insulin, which causes blood sugar levels to rise (above 200mg/dl).

• **Secondary diabetes** is due to causes like pancreatectomy, drugs (Dapsone, rifampin, niacin or nicotinic acid, beta-blockers and calcium channel blocker), and non-pancreatic diseases (Celiac and Crohn disease)

• **Gestational diabetes** is a form of diabetes that develops while a woman is pregnant.[3]

Diabetes Insipidus

Diabetes insipidus may be a rare disorder in which there is an imbalance in the secretion of antidiuretic hormone (ADH). ADH also called vasopressin that controls the amount of water the kidneys excrete in the urine. While a normal person can excrete 1 to 3 quarters of urine a day, people with diabetes excrete up to twenty quarters of urine a day. People with this disorder got to urinate frequently, called polyuria. They may also feel thirsty frequently and consume more liquids, a condition called polydipsia. It's also called central Diabetes insipidus, pituitary Diabetes insipidus, hypothalamic Diabetes insipidus, neuro-hypophyseal-diabetes insipidus, or neurogenic Diabetes insipidus.[4]

There are 4 main types of Diabetes Insipidus:

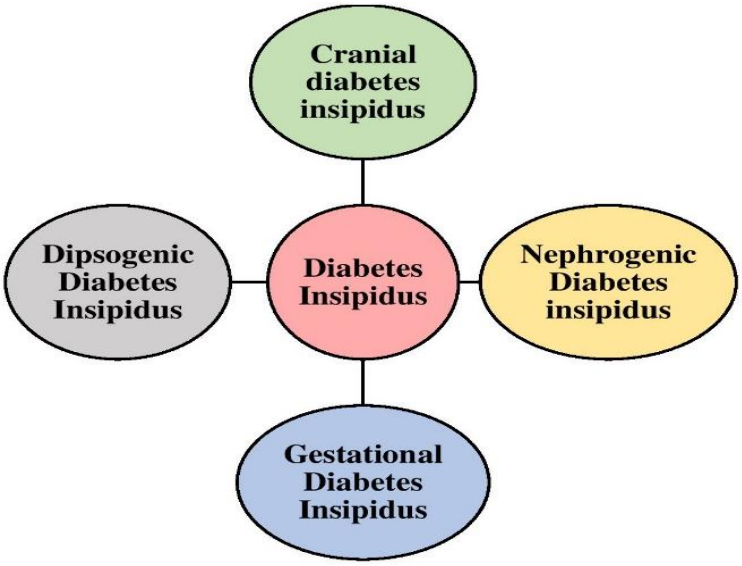


Figure-1: Types of Diabetes Insipidus.[5]

Insulin

Insulin is a peptide hormone produced by the beta-cells of the pancreatic islets of Langerhans and is responsible for facilitating cellular glucose uptake and regulating carbohydrate, lipid, and protein metabolism. Through its mitogenic effects, it promotes cell division and cell growth.

Mechanisms of action of Insulin

It works by attaching directly to its receptors on cell plasma membranes. These receptors are found

on every cell, although their density varies depending on the cell type, with hepatic cells and adipocytes having the highest density.[6]

The insulin receptor is a heterotetrameric glycoprotein that is made up of two subunits: alpha(α) and beta(β). Insulin binding sites can be found on the extracellular alpha subunits. Tyrosine kinase activity is seen in the trans-membranous beta-subunits.[7]

When insulin binds to the alpha subunits, it triggers the beta subunits of tyrosine kinase activity, causing glucose transporters to translocate from the cytoplasm to the cell's surface.[8] These glucose transporters allow the influx of glucose from the blood into the cell, thus reducing the blood glucose levels.[9]

Effects of Insulin in the cells

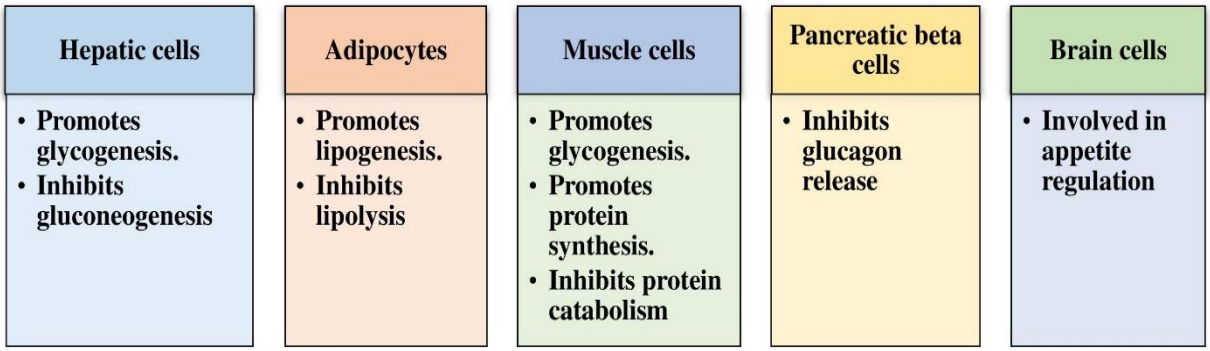


Figure-2: Effects of Insulin in the cells.[10]

Based on the duration of action. Insulin preparation may be grouped as

- Rapid-acting insulin analogs
  Insulin Lispro (3-5 hr)
  Insulin Aspart (3-5 hr)
  Insulin Glulisine (1-2 1/2 hr)
- Short-acting insulins
  Regular/plane (5-8 hr)
- Intermediate-acting insulins
  Isophane insulin (NPH) (18-24 hr)
  Insulin zinc suspension/ Lente
- Long-acting insulin analogs
  Insulin glargine (20-24 hr)
  Insulin Detemir (Up to 24 hr)
  Insulin Degludec (42 hr)
- Insulin Mixture

Combination of 20%-50% regular rapid-acting analogs with 50%-80% NPH analogs and longer-acting analogs. (14-20 hr).[11]

Thickness of the Skin

The skin is the first barrier a needle must overcome when administering an injection or infusion. Skin thickness varies between 1.25 and 3.25 mm in 90% of people, with an average thickness of 2.0 to 2.5 mm. Children's skin is slightly thinner. In both infants and adults, even the thinnest needles (4 mm) reliably pierce the epidermis and enter the subcutaneous fat.[12] To test the feasibility of injecting intramuscularly, measure the distance between the skin's surface and the muscle fascia'.[13]

The abdomen, thigh, and buttock, as well as the upper arm,[14]are ideal injection and infusion sites.

Various Routes of Insulin Administration

Insulin can be administered subcutaneously, intravenously, intraperitoneally, or transdermally. The route of administration is usually determined by the condition and setting of the patient.

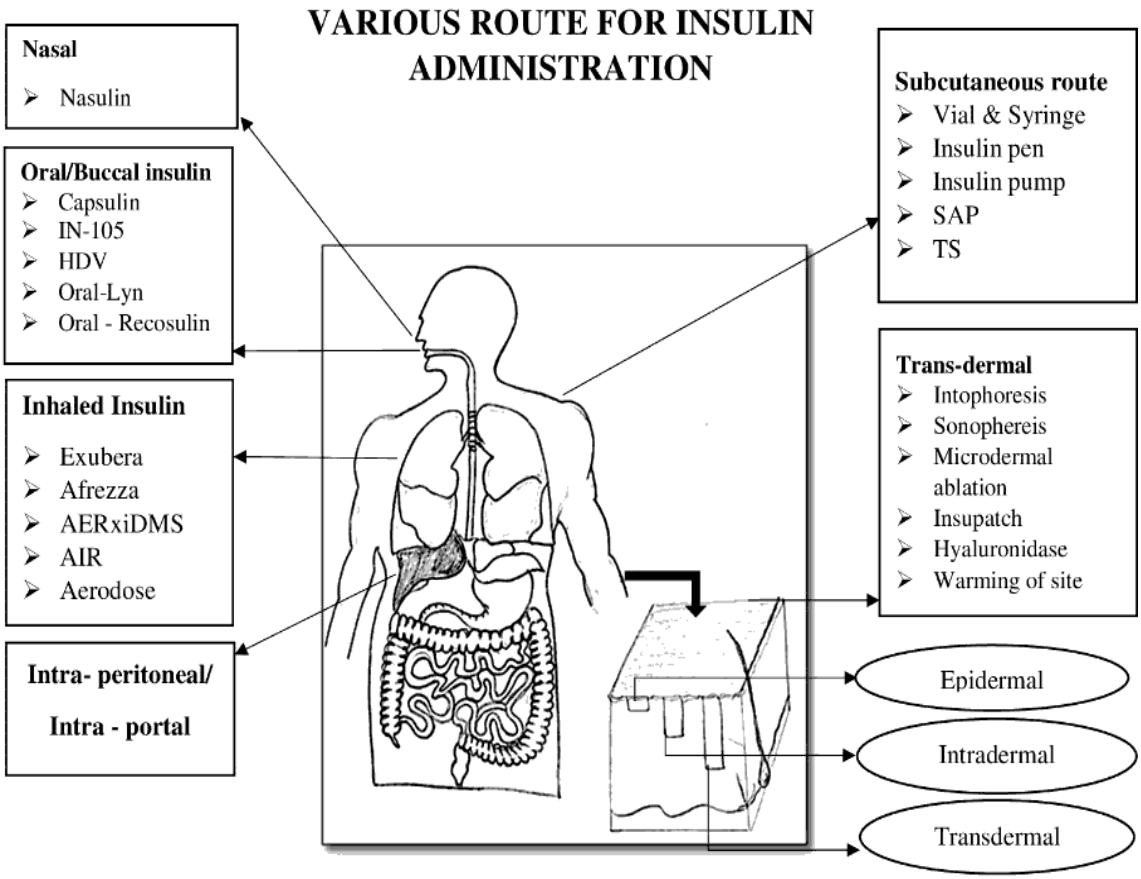


Figure-3: Various routes of insulin administration.[15]

Intraperitoneal

Insulin delivery through the intravenous and subcutaneous routes is associated with peripheral hyperinsulinemia and has been considered non-physiological. Insulin is delivered directly into the portal vein, simulating a high level of insulin in the portal vein.[16]

The pump is implanted beneath the subcutaneous tissue in the lower abdomen under general anaesthesia. From this subcutaneous pocket, the peritoneum is opened, and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, the pump reservoir is refilled in the outpatient clinic transcutaneous at least every 3 months, depending on the individual insulin requirement.[17]

Trans-Dermal Insulin

The problems associated with needles and injections are eliminated with transdermal insulin delivery, and the enormous surface area of the skin makes it a convenient route for insulin delivery. The stratum corneum,the skin's outermost layer, however, prevents insulin from penetrating. Numerous methods have been explored to overcome the barrier of the stratum corneum.[18]

Intravenous Insulin

Intravenous insulin therapy is a process that uses an intravenous infusion of insulin to treat elevated blood sugar (hyperglycemia). Only selected critically ill patients with a diabetes emergency or other conditions affecting blood sugar who require rapid and efficient treatment of hyperglycemia are given intravenous insulin in a hospital ICU setting. Intravenous insulin therapy is only administered under medical supervision, with glucose levels and other vital parameters to be continuously monitored. Human regular insulin is

the only form of insulin that can be delivered intravenously. In intravenous insulin delivery, a rapid-acting insulin analog is not required because the insulin is administered directly into the bloodstream and it has an immediate effect.[19]

Subcutaneous Insulin

Insulin is injected into the fat layer subcutaneously, or beneath the skin. In this form of injection, a small needle is used to inject insulin into the fatty layer between the skin and the muscle. A lifted skinfold technique can be used to elevate the subcutaneous layer away from the underlying muscle (pinching or bunching the skin). This method, if used properly, reduces the risk of unintentional intramuscular injection.[20]

❖ **Dosage Forms of Subcutaneous Insulin**

Individualization of human insulin dosage is essential to produce the optimum outcomes based on blood and urine glucose test results, which is always expressed in United States Pharmacopeia units (USP).

Following are some of the common insulin delivery devices that are used

- Syringes And Vial
- Insulin Pen
- Insulin Pump
- Sensor-Augmented Pump.[21]

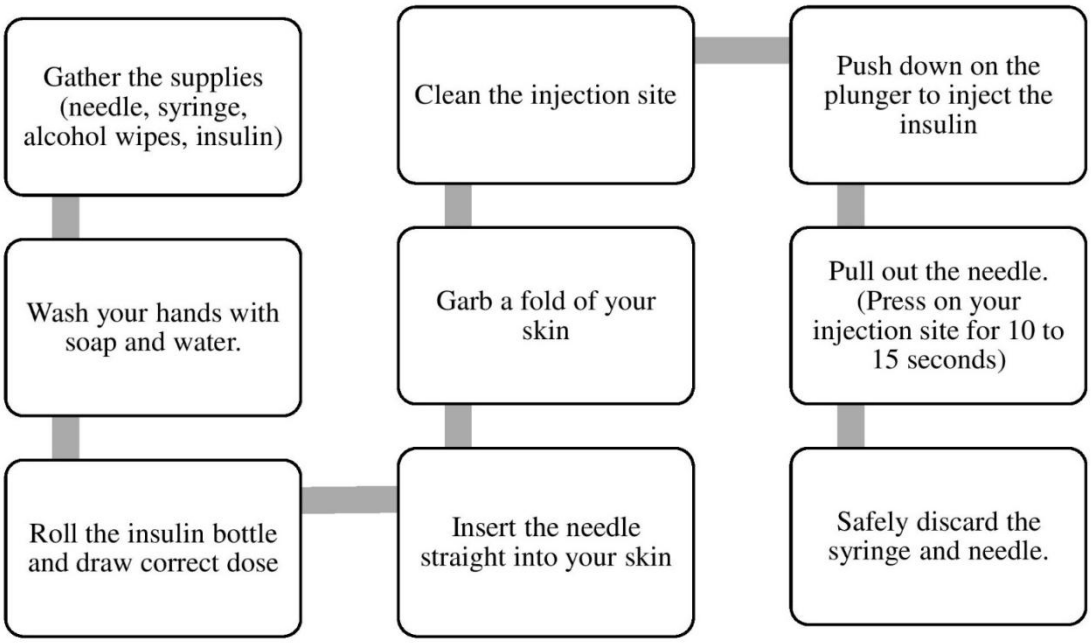
I. Syringes and Vial

SYRINGES differ in terms of the amount of insulin they hold and the needle size. They're made of plastic it should only be used once. Insulin needles have traditionally been 12.7 millimeters (mm) in length. According to recent research, needles as small as 8 mm, 6 mm, and 4 mm are as effective, regardless of body mass. As a result, insulin injections are less painful than in the past.[22]

Dosage of syringes and vial

The traditional method of insulin administration is subcutaneous injection with syringes marked in insulin units. The way units are expressed varies depending on the size of the syringe and the manufacturer. Insulin syringes are available in 0.3mL, 0.5mL, 1mL, and 2mL volumes. Blood glucose should be monitored while switching from one length to another to see if insulin absorption varies.[23]

How to use[24]



Advantages of syringes and vial

- Economically feasible

Disadvantages of syringes and vial

- Syringecauses more pain while administration.
- It is inconvenient to carry
- Inaccurate administration of dose.[25]

II. Insulin Pen

The 'Novolet,' the world's first disposable, prefilled insulin pen, was introduced by Novo in 1989. Pens, rather than syringes, deliver insulin in a simple, accurate, and convenient manner. An insulin pen is composed of three parts: an insulin cartridge, a disposable short needle, and one-clicker unit dosing system. The device can be reusable or disposable. Reusable insulin pens have a cartridge that can be replaced. A prefilled cartridge inside a disposable pen can be used and then discarded.[26]

Pens, as compared to syringes, offer greater flexibility, accuracy, discretion, and long-term cost-effectiveness, resulting in better treatment persistence and adherence. As a result, insulin pens provide better glycaemic control and becoming more popular.[27-28]

Table-1: Details of a few insulin pens in the market.[26]

BRAND NAME	COMPOSITION	COST	MANUFACTURED BY
INSULATARD NOVOLET PEN	Insulin Isophane (100IU)	₹.287.27	Novodisk India Pvt Ltd
HUMANLOG JUNIOR KWIK PEN	Insulin Lispro (100IU)	₹814.32	Eli Lilly and Company India Pvt Ltd
HUMALOG PEN KWIK PEN 200IU/ml	Insulin Lispro (200IU)	₹.1243	Eli Lilly and Company India Pvt Ltd
TRESIBA FLEX TOUCH 100IU/ml	Insulin Degludec (100IU)	₹.1456.5	Novo Nordisk Pharma India Ltd
TOUJEO SOLO STAR 300U/ ml	Insulin Glargine (300u/ml/)	₹.1483	Sanofi India Ltd.
HUMANLOG KWIK PEN 200u/ml	Insulin Lispro (200IU)	₹.1243	Eli Lilly and Company India Pvt Ltd

Junior Kwik Pen, a prefilled half-unit insulin pen that is lighter and smaller than other half-unit insulin pens in the market, was approved by the FDA in 2017.[26] Aside from the 100 U/ml insulin pens that have been in use for decades, new insulin pens for 200 U/ml (Humalog, Tresiba) and 300 U/ml (Toujeo/Glargine) have been developed as a result of advances in the development of higher concentrated insulin. Since 2017, Eli Lilly's Humalog 200 U/ml KwikPen, Novo Nordisk's Tresiba 200 U/ml Prefilled FlexTouch, and Sanofi's Gla-300 SoloSTAR injector pen have all been on the market.[29-31]Needles with lengths of 4 mm, 5 mm, 6 mm, 8 mm, and 12.7 mm are being used in these insulin pens. The Nano 4-mm pen needle (BD), the shortest pen needle, is more comfortable and convenient to use. These needles require less thumb force and allow for a higher flow rate and insulin absorption.[32]

Types of insulin pens

- A prefilled insulin pen cartridge is contained in a disposable pen. The entire pen unit is discarded once it has been used.
- A reusable insulin pen with an insulin cartridge that can be replaced. When a cartridge is empty, it is discarded and a new one is installed.

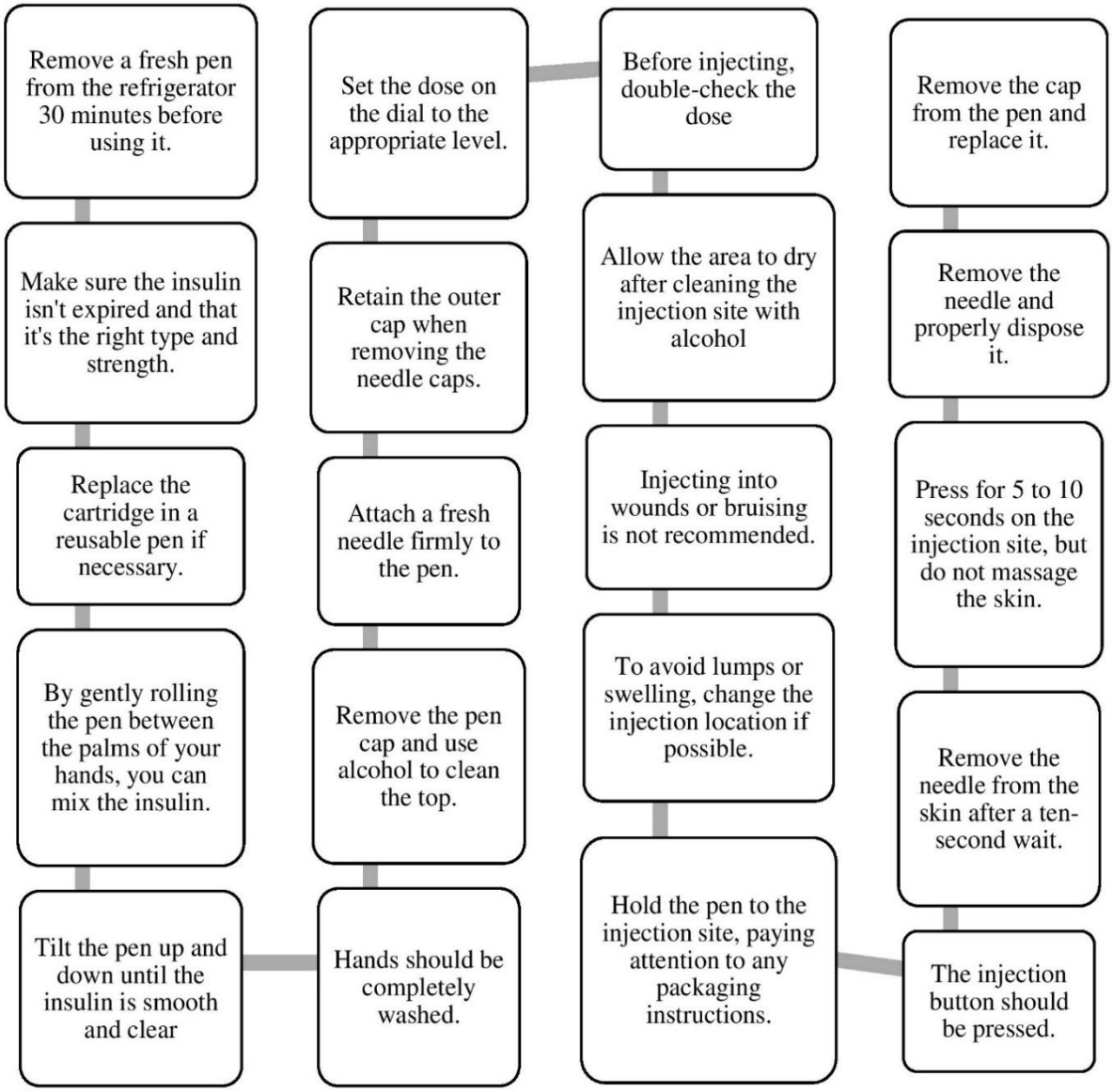
Advantages of insulin pens

- The pen is already prefilled so there is no need to draw insulin through a needle
- They are ready to use and easy to carry
- It's painless and easier to set the right dose

Disadvantages of insulin pens

- More expensive
- It is not possible to blend different insulin kinds
- Some insulin is wasted if the device has to be primed before injecting.[26]

Insulin pens admiistration[33]



III. Insulin Pumps

Insulin pumps are used to provide insulin to achieve precise blood sugar control and lifestyle flexibility while minimizing the symptoms of low blood sugar (hypoglycemia). The insulin pump allows the user to provide a "bolus" during meals to meet the increased demands of carbohydrate consumption.[34]

Insulin pumps can make it much easier for diabetes patients to keep track of their blood sugar levels. Insulin dosages are administered at predetermined intervals by this kind of device. For many people, insulin pumps are a more flexible option than insulin pen injections. Insulin pumps do not have to be used indefinitely, and your insulin control strategy can be changed at any

moment.[35]The pump is now the closest thing on the market to an artificial pancreas.[34]

Types of insulin pumps

- **Tethered Pump**

Insulin pumps that are connected to the cannula have a length of flexible tubing between the pump and the cannula (the short, thin tube which goes through the skin).

The pump, which is usually provided with controls, can be tucked into pockets or carried in pump pouches which can be worn under or outside of clothing.

Commonly available examples of tethered pumps include **Accu-Chek Spirit Combo[36]Animas Vibe [37]Medtronic MiniMed Paradigm Veo.**[38]

- **Patch Pump**

Patch pump has no extra tubing, which means the pump sits directly on your skin and it works by using a remote.[39]

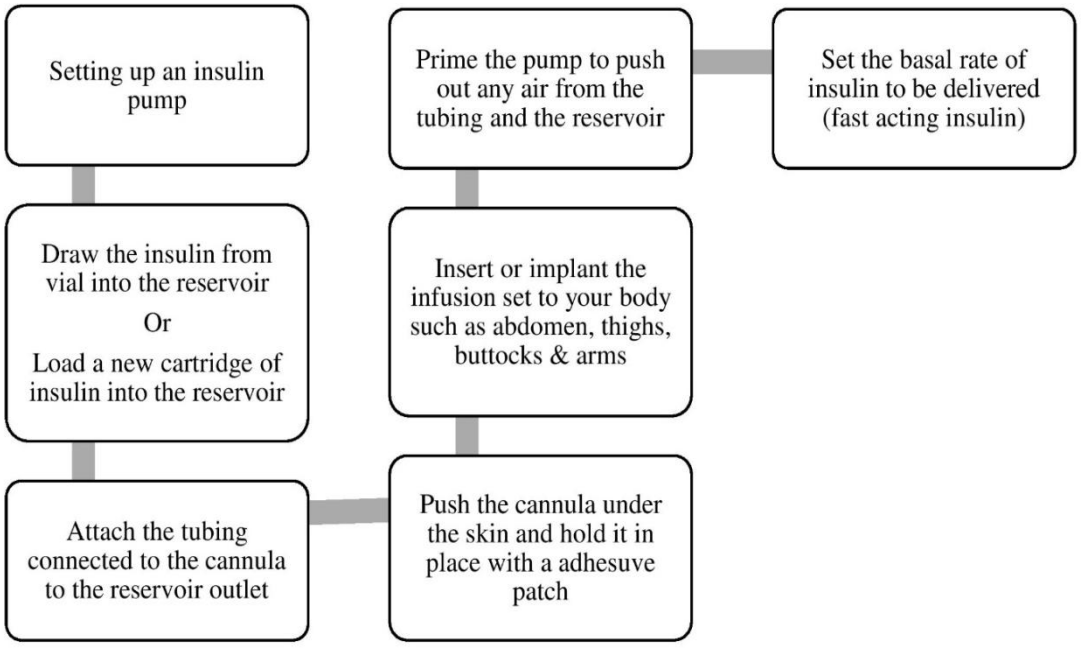
- **Implanted Insulin Pump (IIP)**

An insulin pump is surgically implanted and remains in the body for the rest of its life.An insulin pump placed in the abdomen can inject insulin into the peritoneal cavity, which has a lot of blood capillaries and can absorb insulin quickly.[40]

- **Closed-Loop Insulin Pump (Artificial Pancreas)**

Closed-loop insulin pumps often called "artificial pancreas,"[41] are insulin pumps that are linked together to respond automatically to signals from a continuous glucose monitor that the patient must wear all day.

Insulin pumps administration[42]



Advantages of insulin pumps

Many people choose insulin pumps because they offer:

- Consistent, adjustable insulin delivery.
- Fewer insulin injections.
- Flexibility and privacy.
- Improved blood sugar levels.

Disadvantages of insulin pumps

Possible cons of using an insulin pump can include:

- Inability to hide the tubing or pump with non-patch styles.
- Higher cost than injections.
- Pumps breaking or tubing becoming disconnected.

It's also possible to place the pump incorrectly. It's vital to understand how to use an insulin pump and to monitor your blood sugar levels periodically. If you don't, you risk not getting enough insulin, which can be hazardous and even fatal. If you're a first-time user, ask your healthcare provider for setup instructions.[43]

Continuous Subcutaneous Insulin Infusion Pump

A battery-operated, portable, programmable pump delivers rapid-acting insulin through a subcutaneous infusion set in the continuous subcutaneous insulin infusion system. The basal insulin infusion rate can be temporarily adjusted by a fixed percentage upwards or downwards at least once every hour. Various basal rate profiles can be recorded and used in different situations.[44]

The Diabetes Specialist Team supports the use of CSII in Type 1 diabetes self-management. This group should include a diabetologist, a diabetes specialist nurse, and a dietician. The multidisciplinary pump team should choose whether or not to start insulin pump therapy.[45]

Advantages of continuous subcutaneous insulin infusion pump.[46]

- More flexibility with insulin dosing and timing
- Potential for multiple insulin doses per meal
- Smart pump functions: insulin on-board, time alarms, and bolus calculator options

Disadvantages of continuous subcutaneous insulin infusion pump

- More costly
- The potential risk for site infection, dislodgement, and subsequent ketosis
- Large insertion needles.

IV. Sensor-Augmented Pump

Integrated sensor-augmented pump (SAP) therapy systems combine continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion to help people with Type 1 diabetes improve their glycaemic control and quality of life. When hypoglycaemia develops or is detected, SAP systems that interrupt insulin supply have been proven to minimize the frequency and severity of hypoglycaemia.[47]

While CSII has obvious benefits and modern insulin pumps are extremely safe, structured patient education at the start of pump therapy, as well as ongoing support and refresher education to enable effective use of CSII, is critical to ensuring that glycaemic control is optimized and that the user can recognize any pump insulin delivery failure and take appropriate action to maintain safe glycaemic control.[48]

Conclusion

Insulin cannot control blood sugar on its own; it must be used with a well-balanced diet and frequent exercise, as well as any recommended drugs. There has been a long history of studies on developing a minimally or non-invasive insulin delivery system that is effective, safe, convenient, and socially accessible. Each insulin delivery and distribution technique has its benefits and drawbacks. Successful, alternative delivery systems could enhance diabetes treatment and improve patients' quality of life. In comparison to a typical vial or syringe, the insulin pen was

proved to be significantly easier to use and less unpleasant. Insulin pens are easy to use and have the potential to improve patient satisfaction and therapeutic adherence. Some characteristics of an insulin pen may make it more suitable for certain patients, and physicians must be aware of these requirements.

Acknowledgement

We would like to pay our deepest gratitude and special thanks to our principal Dr.G. Murugananthan and Dr.P. Sharmila Nirojini Professor and head of department of pharmacy practice for their support and guidance to complete this review.

Summary

Diabetes is a chronic, metabolic disorder characterized by high levels of blood glucose (or blood sugar), which may lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. Hyperglycaemia is a symptom of diabetes, which is caused by a defect in insulin secretion, insulin action, or both. Inadequate insulin secretion and/or decreased tissue responses to insulin causes insulin deficiency at one or more points along the complex hormone action pathways.In intravenous insulin delivery, a rapid-acting insulin analog is not required because the insulin is administered directly into the bloodstream and it has an immediate effect. Junior KwikPen, a prefilled half-unit insulin pen that is lighter and smaller than other half-unit insulin pens in the market, was approved by the FDA in 2017. Aside from the 100 U/ml insulin pens that have been in use for decades, new insulin pens for 200 U/ml (Humalog, Tresiba) and 300 U/ml (Toujeo/Glargine) have been developed as a result of advances in the development of higher concentrated insulin. Insulin pumps are used to provide insulin to achieve precise blood sugar control and lifestyle flexibility while minimizing the symptoms of low blood sugar (hypoglycemia). For many people, insulin pumps are a more flexible option than insulin pen injections.An insulin pump placed in the abdomen can inject insulin into the peritoneal cavity, which has a lot of blood capillaries and can absorb insulin quickly.40 Closed-loop insulin pumps often called “artificial pancreas,” are insulin pumps that are linked together to respond automatically to signals from a continuous glucose monitor that the patient must wear all day.A battery-operated, portable, programmable pump delivers rapid-acting insulin through a subcutaneous infusion set in the continuous subcutaneous insulin infusion system. While CSII has obvious benefits and modern insulin pumps are extremely safe, structured patient education at the start of pump therapy, as well as ongoing support and refresher education to enable effective use of CSII, is critical to ensuring that glycaemic control is optimized and that the user can recognize any pump insulin delivery failure and take appropriate action to maintain safe glycaemic control.In comparison to a typical vial or syringe, the insulin pen was proved to be significantly easier to use and less unpleasant. Some characteristics of an insulin pen may make it more suitable for certain patients, and physicians must be aware of these requirement**.**

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