WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 11, 1054-1069. Review Article ISSN 2277– 7105

INSULIN THERPY

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Article Received on
12 July 2021,

Revised on 1 Aug. 2021,
Accepted on 21 Aug. 2021,

DOI: 10.20959/wjpr202111-21532

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ABSTRACT

Insulin is the one greatest medical discoveries that saved billions of people's in patients with Diabetes. Insulin is lifesaving medication option most of the patient with Type 2 Diabetes take insulin injection to control elevated blood sugar levels so today we will discuss about what is insulin? Features of insulin type of insulin, starting dose of insulin problem, insulin in disease manily DIABETES MELLITUS. Natural ways to improve insulin sensitivity, etc. Since the introduction of insulin analogs in 1996, insulin therapy options for type 1 and type 2 diabetes have expanded. Insulin therapies are now able to more closely mimic physiologic insulin secretion and this achieve better glycemic control in patients with diabetes. The chapter reviews the pharmacology of available insulin, type of insulin regimes, and Principles of Dosage selection and adjustment and provide an overview of insulin, type of therapy. Instability of the body to Synytheszie insulin of human cells resistance leads to a condition called Diabetes mellitus which characterized by chronic hyperglycemia. There are two types of diabetes type 1, type 2.

KEYWORD*:* Structure of insulin, What is insulin?, discovery of insulin, difference type of insulin, starting dose of insulin, insulin problems, insulin therapy, features of therapy, adverse effects, insulin in diseases, natural ways to improve insulin sensitivity , futures prospects of insulin therapy.

INTRODUCTION

Diabetes Mellitus is a disease that occurs when your blood glucose, also called sugar, is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin a hormone made by pancreas, helps glucose from food get into your cell to be used for energy. Sometimes your body doesn't make use insulin well. Glucose then stays in your blood and doesn't reach your cells. Over time having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can steps to manage your diabetes and stay healthy. Sometimes people call diabetes " a touch of sugar "or "borderline diabetes". These terms suggest that someone doesn't really have diabetes or has a less serious case, but every case of diabetes is serious.

- Type 2 diabetes – A chronic conditions that affects the way the body process blood sugar (glucose).
- Type 1 diabetes – A chronic conditions in which the pancreas produces little or no insulin.
- Prediabete - A conditions in which blood sugar is high, but not high enough to be type 2 diabetes.

- ***Insulin***

In 1922, Canadian researchers were the first to demonstrate a physiologic response to injected animal insulin in a patient with type 1 diabetes. In 1955, insulin was the first protein to be fully sequenced. The insulin molecule consists of 51 amino acids arranged in two chains, an A chain (21 amino acids) that are linked by two disulfide bonds (Figure 1). Proinsulin is the insulin precursor that is transported to the Golgi apparatus of the beta cell where it is processed and packaged into granules. Proinsulin, a single-chain 86 amino acid peptide, is cleaved into insulin and c-peptide.

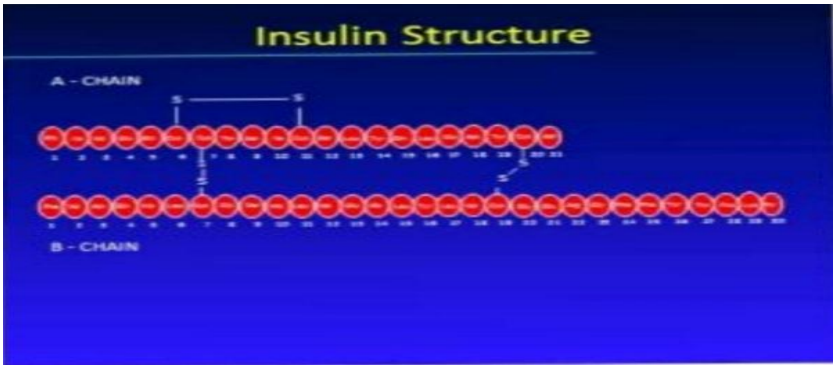


Figure 1: Insulin Structure.

- ***What is insulin?***

Insulin is a hormone that is responsible for allowing glucose in the blood to enter cells, providing them with the energy to function. A lack of effective insulin plays a key role in the development of diabetes. Hormones are chemical messengers that instruct certain cells or tissues to act in a certain way that supports a particular function in the body. Insulin is a chemical messengers that allows cells to absorb glucose, a sugar, from the blood. The pancreas is an organ behind the stomach that is the main source of insulin in the body. Clusters of cells in the pancreas called islets produce the hormone and determine the amount based on blood glucose levels in the body. The higher the level of glucose, the more insulin goes into production to balance sugar levels in the blood.Insulin also assists in breaking down fats or proteins for energy.

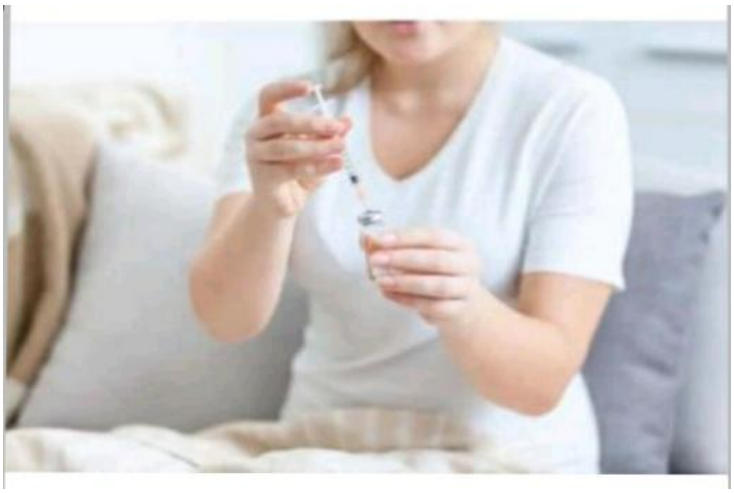
- ***Discovery of insulin***

Insulin was discovered by Sir Frederick G Banting (pictured), Charles H Best and JJR MacLeod at the university of Toronto in 1921 and it was subsequently purified by James B Collip.

Before 1921, it was exceptional for people with **type 1 diabetes** to live more than a year or two. One of the twentieth century's greatest medical discoveries, it remains the only effective treatment for people with type 1 diabetes today.

This means that in 2021, we're celebrating 100 years since the discovery of insulin. It was one of the greatest medical breakthroughs in history, which went on to save millions of lives around the world and triggered a century of **diabetes discoveries.** Here we take a look at journey that got us there.

Be the first to hear about our celebrations in 2021 and beyond, through our **monthly enewsletter.**



- ***Types of insulin***

A person can take different types of insulin based on how long they need the effects of the supplementary hormone to last.

People categorize these types based on several different factors:

- Speed of onset, or how quickly a person taking insulin can expect the effects to start.
- Peak, or the speed at which the insulin reaches its greatest impact.
- Duration, or the time it takes for the insulin to wear off.
- Concentration, which in the United States is 100 units per milliliter. (U100)
- The route of delivery, or whether the insulin requires injection under the skin, into a vein, or into the lungs by inhalation.

Intermediate-acting insulin

This type enters the bloodstream at a slower rate but has a longer-lasting effect. It is most effective at managing blood sugar overnight, as well as between meals.

Option for intermediate-acting insulin include:

- **NPH human insulin:** this takes between 1 and 2 hours to onset, and reaches its peak within 4 to 6 hours. It can last over 12 hours in some cases. A very small dose will bring forward the peak effect, and a high overall duration of its effect.
- **Pre-mixed insulin:** this is a mixture of NHP with a fast-acting insulin, and its effects are a combination of the intermediate and rapid-acting insulins.

Long-acting insulin

While long-acting insulin is slow to reach the bloodstream and has a relatively low peak, it has a stabilizing "plateau" effect on blood sugar that can last for most of the day.

It is useful overnight, between meals, during fasts.

❖ ***Different Types of Insulin***

1. **Onset**

   Before the insulin hits your bloodstream

2. **Peak**

   Insulin is at a peak in bloodstream

3. **Duration**

   Length of time insulin is in bloodstream

4. **Rapid Acting**

   Insulin reaching bloodstream within 15 minutes

5. **Short Acting**

   Insulin reaches bloodstream within 30 minutes

6. **Intermediate Acting**

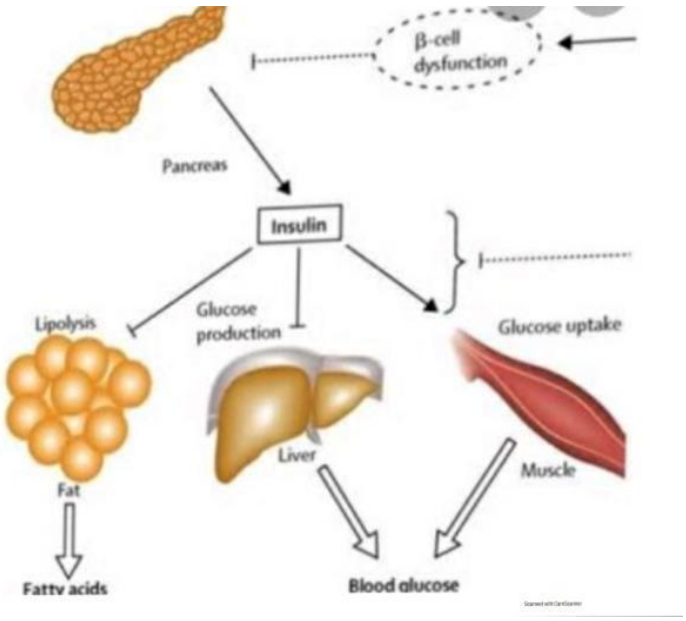
   Insulin with NHP to control glucose for 10-12 hours

7. **Long acting**

   This can be effective for as long as 24 hours

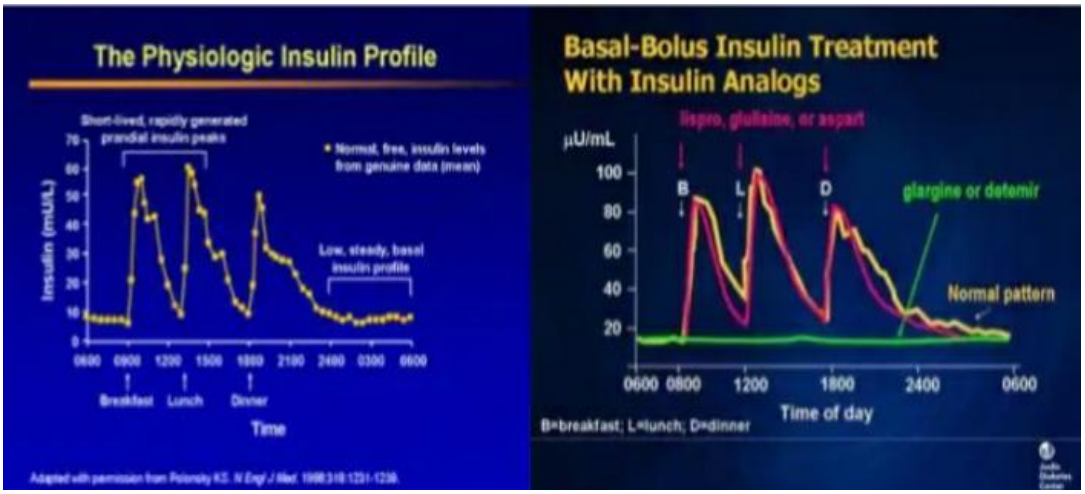
8. **Premixed**

   A mix of rapid short, and intermediate insulin



❖ **Types of insulin**

Rapidò-Acting	Onset	Peak	Duration	Role in Blood Sugar Management
Aspart Lispro Glulisine	10-20 min. 15-30 min. 20-30 min.	40-50 min. 30-90 min 30-90 min.	3-5 hours 3-5 hours 1-2[5]/2 hours	Covers insulin needs for meals eaten at the same time as the injection



Starting dose of insulin

T1DM: 1-0.2-1 U/kg/day[1]

T2DM: 0.2-0.3 U/kg/day

❖ In split mixed regimen- 2/3 as intermediate acting and 1/3 as short-acting.

❖ In basal bolus regimen: ½ basal at bed time and ½ bolus in 3 divided doses.

❖ Dosage is individualized and titrated soon.

❖ ***Insulin problems***

In some Diabetes people, the immune system attacks the islets, and they cease to produce enough.

When this occurs, blood glucose stays in the blood cells cannot absorb them to convert the sugars into energy.

This is the onset of type 1 diabetes, and a person with this version of diabetes will need regular short of insulin to survive.

Type 2 diabetes will develop when the islets cannot produce enough insulin to overcome insulin resistance.

Since the early 20th century, doctors have been able to isolate insulin and provide it in an injectable form to supplement the hormone for people who cannot produce if themselves or have increased insulin resistance.

❖ ***Diabetes Mellitus***

is a disease that occurs when your blood glucose, also called sugar, is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin a hormone made by pancreas, helps glucose from food get into your cell to be used for energy. Sometimes your body doesn't make use insulin well. Glucose then stays in your blood and doesn't reach your cells. Over time having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can steps to manage your diabetes and stay healthy. Sometimes people call diabetes "a touch of sugar "or "borderline diabetes". These terms suggest that someone doesn't really have diabetes or has a less serious case, but every case of diabetes is serious.

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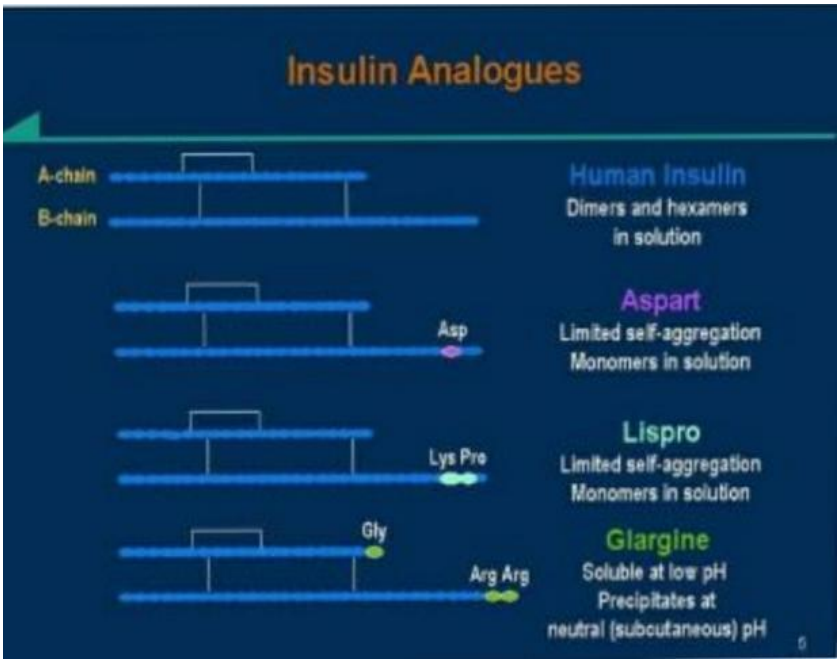
❖ ***Insulin therapy***

- ❖ Insulin should be given to all patients with type 1 diabetes
- ❖ Insulin therapy FOR TYPE 2 DIABETES
- ❖ Consider initiating combination insulin injectable therapy when blood glucose is>300-350mg/dL and /or AIC is > 10 -12%%.
- ▪ Prevent and treat fasting and postprandial hyperglycemia.
- ▪ Permit appropriate utilization of glucose and other nutrients by peripheral tissues.
- ▪ Suppress hepatic glucose production.
- ▪ Prevent acute complications of uncontrolled diabetes.
- ▪ Prevent long term complications of chronic diabetes.



❖ ***The future of insulin therapy***

An Example

❖ **Mr. M:58 yo with history type 2 diabetes for 8 years**

➢ In addition to oral meds, he is on 70/30 insulin: 30 u AM and 15 u AM

➢ Current total daily dose = 45 u of 70/30

➢ However, he has been having difficulty with wide glycemic excursions

❖ **After discussing his options in detail, he is willing to begin basal/bolus regimen**

➢ **New TDD = 45 u × 75 = 33.75 =34 u**

➢ **Basal =** 17 u Lantus at bedtime

➢ **Bolus =**17 u total / 3 = 5.6 u = 5 u Humalog with meals

❖ ***Adverse effects***

Disorders gastrointestinal events, hypoglycemia, injection site reactions and musculoskeletal complaints.

The major clinical studies on insulin showed that the safety and effectiveness of human biosynthetic insulin and animal-sourced insulin are comparable. In addition, the number and types of adverse reactions reported with both types of insulins were Similar. In fact, adverse reactions such as hypoglycemia, may occur while taking either type of insulin without any major difference.

Hyperglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, distributed behavior, hunger, loss of consciousness, or in extreme circumstances even death and can occur without recognizable symptoms.

Several types of hype of hypersensitivity reactions to insulin preparations have been described. These reactions may be caused by the insulin itself or by additives within the preparation. Hypersensitivity reactions to insulin are rare with human insulins and insulin analogues. However, some types of reactions are serious and even life-threatening and may have a significant detrimental Impact on the patient's diabetes management. Local reactions may present as erythema, swellings, heat, or subcutaneous nodules. They usually occur within the first two weeks of therapy, then disappear. Immunologic responses to insulin, particularly animal Insulin formulations, include the formation of anti-insulin antibodies.

❖ ***Insulin in diabetes***

- ***Diabetes mellitus***

This is an all- encouraging term for hyperglycemia or excessive blood sugar. There are further classifications of diabetes mellitus. These include:

➢ Type 1 diabetes or insulin dependent diabetes mellitus (IDDM) – in these patients there are auto-immune mechanisms in which the body's own immune cells attack the insulin producing beta cells of the pancreas. This leads to an absolute insulin deficiency. These patients need to be supplemented with insulin injections from outside.

➢ Type 2 or Non insulin dependent diabetes mellitus (NIDDM) – this is a condition where the body fails to produce the required amount of insulin. Thus there is a relative insulin deficiency. Genetic susceptibility, environmental factors, obesity, lack of physical exercise, insulin resistance etc. May lead to relative insulin deficiency.

➢ Gestational diabetes – Some pregnant women require more insulin than their body can produce during pregnancy.

- ***In pregnancy***

One trial compared Lispro insulin with regular insulin and provided very low-quality evidence for the outcomes. There were seven episodes of pre- eclampsia in the Lispro group and nine in the regular insulin group, with no clear difference between the two groups. There were five caesarean sections in the Lispro group and nine in the regular insulin group, with no clear difference between the two groups. There were no cases of fetal anomaly in the

Lispro group and one in the regular insulin group, with no clear difference between the groups. Macrosomia, perinatal deaths, episodes of birth trauma including shoulder dystocia, nerve palsy, and fracture, and the composite outcome measure of neonatal morbidity were not reported.

The use of Lispro was associated with lower rates of neonatal jaundice and severe maternal hypoglycemia than regular insulin. Lispro use was also associated with higher birth weight and an increased incidence of large for gastrointestinal age births compared with regular insulin. Rates of cesarean section and macrosomia were Similar in pregnant women treated with as part and regular insulin. Births weights and rates of severe maternal hypoglycemia, respiratory dysfunction syndrome, and neonatal intensive care unit admission were Similar after pregnant women treated with glargine and NHP insulin.

- **Insulinoma**

These are tumors of the pancreatic beta cells that lead to excess production of insulin and this results in hyperglycemia. However, blood glucose level alone is not diagnostic of insulinoma. Fasting insulin level of greater than 24 mU/mL is found in approximately 50% of patients with insulinoma.

Values of insulin greater than 7 mU/mL after a more prolonged fast in the presence of a blood glucose less than 40 mg/ dL also should raise suspicion of insulinomas.

Measurements of Proinsulin and C peptide also have proven to be valuable in patients suspected of having organic hyperglycemia.

- **Metabolic Syndrome**

Metabolic syndrome is a combination of multiple clinical disorders that form a syndrome. It was initially called syndrome X by Gerald Reaven, Reaven's syndrome after Reaven, CHAOS in Australia, and sometimes pre diabetes. The basic underlying cause may be the insulin resistance of type 2 diabetes.

Metabolic syndrome is defined as the presence of any three of the following conditions:

- Waist measurement of 40 inches or more for men and 35 inches or more for women.
- Blood pressure levels of 130/85 or above, or taking medication for elevated blood pressure levels.

- Fasting blood glucose levels of 100 mg / dL or above, or taking medication for elevated blood glucose levels

- **Polycystic Ovary Syndrome**

Polycystic Ovary Syndrome or PCOS is complex Syndrome in women that includes features of anovulation, excess androgens, hirsutism, infertility etc. Most women with PCOS also exhibit features of the metabolic Syndrome, including insulin resistance, obesity and distributed blood lipid or cholesterol levels. There is high risk of type 2 diabetes as well.

Natural ways to improve your Insulin Sensitivity

Insulin is an essential hormones that controls your blood sugar levels.

Here are 14 natural, science baked ways to boost your insulin Sensitivity.

- **1) Get more sleep**

A good night's sleep is important for your health.

In contrast, a lack of sleep can be harmful and increase your risk for infections, heart disease, and type 2 diabetes.

Several studies have also linked poor sleep to reduced insulin sensitivity.

For example, one study involving nine healthy volunteers found that getting just 4 hours of sleep in one night reduced insulin Sensitivity and the ability to regulate blood sugar, compared with getting 8 1/2 hours of sleep.

- **2) Reduce stress**

Stress affects your body's ability to regulate blood sugar.

It encourages the body to go into "fight- or- fight" mode, which stimulates the production of stress hormones like cortisol and glucagon.

These hormones break down glycogen, a form of stored sugar, into glucose, which enters your bloodstream for your body to use as a quick source of energy.

Stress hormones also make the body more insulin resistant. This prevents nutrients from being stored and makes them more available in the bloodstream to be used for energy.

- **3) Eat more soluble fiber**

Fiber can be divided into two broad categories - soluble and insoluble.

Insoluble fiber mostly acts as a bulking agent to help stool move through the bowels.

Soluble fiber also helps feed the friendly bacteria in your gut, which have been linked to increased insulin sensitivity.

For example, a study involving 264 women found that those who ate more soluble fiber had significantly lower levels of insulin resistance.

- **4) Drink more Green Tea**

Green tea is an excellent beverage for your health.

It's also a great choice for people with type 2 diabetes or those who are at risk for it. Several studies have found that drinking green tea can increase insulin sensitivity and reduce blood sugar.

For example, an analysis of 17 studies investigated the effects of green tea on blood sugar and insulin sensitivity.

It found that drinking green tea significantly reduced fasting blood sugar and increased insulin sensitivity.

These beneficial effects of green tea could be due to its powerful antioxidant EGCG, which may studies have found to increase.

- **5) Reduce your intake of added sugars**

There's a big difference between added sugars natural sugars.

Natural sugars are found in sources like plants and vegetables, both of which provide lots of other nutrients.

Conversely, added sugars are found in more highly processed foods. The two main types of sugar added during the production process are high-fructose corn syrup and table sugar, also known as sucrose. Both contain approximately 50% fructose.

❖ ***Future prospects of insulin therapy***

The improved insulin formulation, newer delivery method / routes., and digital technology are rapidly becoming effective and have great potential to improve metabolic control as well as other outcome, including quality of life of person living with diabetes mellitus.

- **Areas of uncertainty –** Despite significant advance, there are still many barrier, challenge, and uncertainty involving insulin therapy. With newer pharmacology and technological approaches, there are many potential drawbacks to be addressed, such as immunogenicity, biocompatible, degradation /clearence of delivery materials, stability, precision of dosing, reproducibility, predictability of performance.
- **Data source –** A literature search of original and review articles, editorials, and metaanalyses in medline/ pubmed and google scholar has been performed. Clinical trials. Gov website was searched for ongoing relevant clinical trials.
- **Therapeutic advances –** New insulin formulation (ultralong basal and ultrapid analogue) we're designed to obtain a prolonged, flatter profile, with less hypoglycemia and improvement of postprandial glucose control, respectively. The next generation of insulin therapy is probably best represented by the "smart" (glucose responsive) insulin, which deliver it according to an endogenous glucose – sensing feedback mechanism. Another area of continues advance includes insulin delivery system with new jet injectors, smart pens, patch pumps, and other needed free device for subcutaneous administration. Many alternative route of insulin delivery (pulmonary, nasal, buccal, oral, transdermal) have also been explored.
- **Newer injectable insulin-** Newer insulin that are promising include long acting basal insulin analogs called insulin Deglucle and ultra fast acting insulin, human insulin Linjeta (formally called VIAject)
- **Insulin degludec-** Insulin degludec, a novel ultra – longacting basal insulin, is almost identical to human insulin in structure except for the last aminoacide deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadexamers after subcutaneous injection, resulting is an ultra – long action profile with half life more than 24 h. Insulin degludec has proven to be non inferior to insulin glargine in clinical trials carried out in both type 1 and type 2 DM. Exploratory studies in type 1 diabetes have shown insulin gegludec to be safe with reduced rates of hypoglycemia and comparable glycemic control to long acting insulin analogs insulin glargine. Phase 3 clinical trials in adult with type 1 DM and type 2 DM glycemic control was comparable to insulin glargine at one year follow up with fewer hypoglycemic episode.

- **VIAject TM –** VIAject is a recombinant human insulin with ultra fast onset of action phrmaco- dynamic and phrmacokinetic studies have shown the onset of action of VIAject is faster than that of human soluble insulin and lispro. VLAject was reported to have less within subject variability of plasma insulin compared to human regular insulin.

CONCLUSION

Inhaled insulin is a novel route of insulin administration which has the potential to become a therapeutic option in the treatment of both TIDM and T2DM. Overall, clinical trials have demonstrated that inhaled insulin is non inferior to subcutaneous insulin for improving glycemic control.

Insulin therapy is often combined with oral agents in patients with uncontrolled type 2 diabetes. For practical purposes, the type of insulin regimen is chosen according to blood glucose profiles. In addition, special consideration in older adults should be given to their cognitive skills, physical and visual limitations, living situations, available resources, and comorbidities. It is advisable to start low and to go slowly on insulin titration to avoid hyperglycemia. Which usually manifests differently in older adults. Keeping these considerations in mind will enhance the safety and efficiency of insulin therapy in older adults.

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