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INSULIN AS A DRUG

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ABSTRACT- *Insulin is a heterodimeric peptide connected by three disulfide bonds, and was first found in 1921. Insulin assumes critical parts in starch digestion as well as in anabolic control of proteins and lipids, physical development, and cell multiplication amid improvement. Glucose animates the combination and arrival of insulin in warm blooded animals. In non-mammalian vertebrates the insulinotropic impact of glucose is feeble however that of amino acids is solid, proposing that the significant part of insulin in blood glucose direction is a generally subordinate capacity in vertebrate advancement. The activities of insulin are interceded differentially by means of two receptors (INSR-A and - B) that are on the other hand grafted from a solitary mRNA in warm blooded creatures. In addition, cross breed receptors, which are made out of subunits of INSRs and IGF-IR, are available. Distinctive substrate connectors, for example, IRS proteins are engaged with the flag transduction pathways of insulin activity.*

It is a hormone discharged in the pancreas, an organ inside the stomach area. Uncommon cell called "beta cells" make the insulin. These phones are situated in the piece of pancreas called the "islets". At the point when a man has Type 1 diabetes, there is lost cells which make insulin. The vast majority with diabetes presently utilize human insulin or insulin analogs. The human insulin does not originate from people, but rather has the same "make-up" as human insulin. It is delivered by microscopic organisms (Lilly) or by yeast (Novo-Nordisk) utilizing "hereditary designing". There are no known preferences of one brand of insulin over another brand. The simple insulins have slight changes that influence their action to look like ordinary insulin movement.

Key words: *Insulin, carbohydrate metabolism, proteins and lipids, glucose stimulates, insulinotropic effect, receptors, hybrid receptors, hormones, pancreas, beta cell, islets, analog insulin, and diabetes*

1. INTRODUCTION

Insulin is ordinarily discharged quickly from the beta-cells of the pancreatic islets in light of supplements consumed after a feast. In type 1 diabetes mellitus, there might be a flat out insulin inadequacy as a result of immune system obliteration of the beta-cells. Then again, in type 2 diabetes mellitus, insulin emission is hindered and is deficient to defeat fringe insulin opposition. Insulin arrangements are utilized to supplant the insufficient hormone in the treatment of diabetes, and presently, there is no elective treatment for type 1 diabetes. Insulin is likewise to be utilized as a part of the treatment of sort 2 diabetes when this can't be satisfactorily controlled by orally dynamic antidiabetic drugs. The point of treatment utilizing insulin is to keep up euglycemia (a plasma glucose level of 4– 7 mole/L) without causing hypoglycemia. Nonetheless, great control is hard to accomplish due to the trouble of overseeing insulin in a way that copies physiological insulin emission, with fast crests amid and promptly after a dinner and low, basal focuses between suppers. Insulin arrangements are presently to a great extent in light of human insulin arranged by enzymic alteration of porcine insulin [human insulin (emp)], by synthetic mix of the A and B chains delivered utilizing microscopic organisms hereditarily changed by recombinant DNA innovation [human insulin (crb)], or from an antecedent created by yeast adjusted by recombinant DNA innovation [human insulin (pyr)]. Porcine and cow-like insulins, removed from the suitable pancreas, stay accessible. Insulin analogs have been created that have either a quick beginning and brief term of activity or a moderate beginning and long length of activity. The short-acting analogs were delivered on the grounds that consistent, solvent insulin shapes hexamers in arrangement, which must separate with the goal for insulin to be assimilated from its subcutaneous infusion site. The outcomes in the simple (insulin glargine) taking shape in the subcutaneous infusion site, giving a long deferral in retention. There is incredible enthusiasm for joining such long-acting insulin analogs infused once day by day with the quick beginning, short-acting analogs infused with every feast to give a substantially more physiological plasma insulin profile than could be accomplished utilizing traditional dissolvable insulin together with the long-acting insulin details, for example, protamine zinc insulin or insulin zinc suspensions Owens (2002).

2. Discovery of Insulin

Amid the nineteenth century, perceptions of patients who kicked the bucket of diabetes regularly demonstrated that the pancreas was harmed. In 1869, a German restorative understudy, Paul Langerhans, found that inside the pancreatic tissue that produces stomach related squeezes there were groups of cells whose capacity was obscure. A portion of these cells were in the end appeared to be the insulin-creating beta cells. Afterward, to pay tribute to the individual who found them, the cell bunches were named the islets of Langerhans.

In 1889 in Germany, physiologist Oskar Minkowski and Doctor Joseph von Mering, demonstrated that if the pancreas was expelled from a puppy, the creature got diabetes. In any case, if the channel through which the pancreatic juices stream to the digestive tract was ligated - carefully tied off so the juices couldn't achieve the digestive system - the canine created minor stomach related issues however no diabetes. So it appeared that the pancreas must have no less than two capacities:

- To create stomach related juices
- To deliver a substance that controls the sugar glucose

This theoretical inward emission was the key. On the off chance that a substance could really be segregated, the puzzle of diabetes would be comprehended. Advance, notwithstanding, was moderate.

3. Principle of Insulin

Human insulin is presently delivered by recombinant DNA innovation. Different organizations contrast in their technique however the fundamental important is presentation of human insulin or proinsulin quality into life forms like E coli or Yeast. Yeast based innovation may offer physio-compound basic and protein collapsing focal points however, this may not be clinically important. The life forms continue increasing and thus delivering insulin or proinsulin which is changed over to insulin by enzymatic cleavage.

4. Structure of Insulin

- Human insulin comprises of 51 amino corrosive in two chains associated by two disulfide spans (a solitary quality items cut into 2 chains amid post-translational alteration).
- T1/2~5-10 minutes, debased by glutathione-insulin transhydrogenase (insulinase) which cuts the disulfide joins.
- Bovine insulin contrasts by 3 amino corrosive, pork vary by 1 amino corrosive.
- Insulin is put away in a complex with Zn2+ particles.

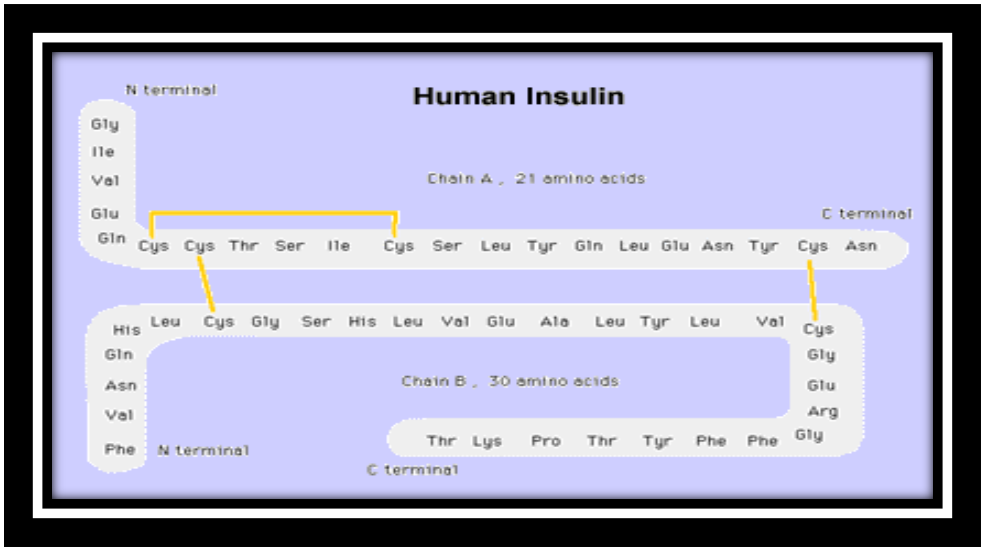

Fig 1: Structure of Insulin

5. What does Insulin do?

Sustenance (starch) is changed over to sugar for the body vitality needs. The insulin enables the sugar to go from the blood into the cells. There it is scorched for vitality. The body can't transform sugar into vitality without insulin. Insulin additionally kills the making of sugar in the liver. On the off chance that insulin isn't accessible, the sugar develops in the blood and spills into the pee. Individuals who have type 1 diabetes can't make enough insulin. These individuals need to get the required insulin through infusions. Insulin can't taken as a pill, on the grounds that the stomach corrosive annihilates it. There are no known vitamins, herbs or different medicines which can replace insulin infusion. Individuals who have type 2 diabetes still make insulin. They can take pills to enable them to make significantly more insulin or to be more touchy to their own insulin. Be that as it may, the pills are not insulin.

6. Types of Insulin

There are four primary sorts of Insulin:

- **Rapid-acting**: Usually taken before a dinner to cover the blood glucose rise from eating. This sort of insulin is utilized with longer-acting insulin.
- **Short-acting**: Usually taken around 30 minutes before a dinner to cover the blood glucose rise from eating. This sort of insulin is utilized with longer-acting insulin.
- **Intermediate-acting**: Covers the blood glucose rises when quick acting insulins quit working. This sort of insulin is frequently joined with quick or short-acting insulin and is normally taken two times every day.
- **Long-acting**: This sort of insulin is regularly consolidated, when required, with fast or short-acting insulin. It brings down blood glucose levels when fast acting insulins quit working. It is taken more than once per day.

Table 1: A guide on Insulin Types for people with Diabetes

Type	Brand Name	Onset (length of the before insulin reaches bloodstream)	Peak (time period when insulin is most effective)	Duration (how long insulin works for)
Rapid- acting	Humalog[H] Novolog[NL] Apidra[AP]	10-30 minutes	30 minutes-3 hours	3-5 hours
Short- acting	Regular[R]	30 minutes-1 hours	2-5 hours	Up to 12 hours
Intermediate-acting	Neutral Protamine Hagedorn[NPH]	1.5-4 hours	4-12 hours	Up to 24 hours
Long- acting	Lantus Levemir	0.8-4 hours	Minimal peak	Up to 24 hours

7. Formation of Insulin Drug

Raw Materials

Human insulin is developed in the lab inside basic microscopic organisms. Escherichia coli is by a long shot the most broadly utilized sort of bacterium, however yeast is likewise utilized.

Scientists require the human protein that produces insulin. Producers get this through an amino-corrosive sequencing machine that incorporates the DNA. Producers know the correct request of insulin's amino acids (the nitrogen-based atoms that line up to make up proteins). There are 20 regular amino acids. Producers input insulin's amino acids, and the sequencing

machine associates the amino acids together. Likewise important to combine insulin are substantial tanks to develop the microscopic organisms, and supplements are required for the microorganisms to develop. A few instruments are important to particular and purge the DNA, for example, an axis, alongside different chromatography and x-beam crystallography instruments.

Manufacturing Process

Blending human insulin is a multi-step biochemical process that relies upon fundamental recombinant DNA procedures and a comprehension of the insulin quality. DNA conveys the guidelines for how the body functions and one little section of the DNA, the insulin quality, codes for the protein insulin. Producers control the natural forerunner to insulin with the goal that it develops inside straightforward microorganisms. While makers each have their own particular varieties, there are two essential techniques to fabricate human insulin.

Working with Human Insulin

1. The insulin quality is a protein comprising of two separate chains of amino acids, A over a B chain that are held together with securities. Amino acids are the fundamental units that manufacture all proteins. The insulin a chain comprises of 21 amino acids and the B chain has 30.
2. Before turning into a functioning insulin protein, insulin is first delivered as preproinsulin. This is one single long protein chain with the A and B chains not yet isolated, a segment in the center connecting the chains together and a flag grouping toward one side advising the protein when to begin emitting outside the cell. After preproinsulin, the chain develops into proinsulin, still a solitary chain however without the flagging succession. At that point comes the dynamic protein insulin, the protein without the area connecting the A and B chains. At each progression, the protein needs particular catalysts (proteins that complete compound responses) to create the following type of insulin.
3. One technique for assembling insulin is to develop the two insulin chains independently. This will abstain from assembling every one of the particular chemicals required. Makers require the two smaller than normal qualities: one that creates the A chain and one for the B chain. Since the correct DNA grouping of each chain is known, they integrate every short quality's DNA in an amino corrosive sequencing machine.
4. These two DNA particles are then embedded into plasmids, little round bits of DNA that are all the more promptly taken up by the host's DNA.
5. Producers first embed the plasmids into a non-destructive kind of the bacterium E. coli. They embed it by the lacZ quality. LacZ encodes for 8-galactosidase, a quality broadly utilized as a part of recombinant DNA strategies since it is anything but difficult to discover and cut, enabling the insulin to be promptly expelled with the goal that it doesn't lose all sense of direction in the bacterium's DNA. By this quality is the amino corrosive methionine, which begins the protein development.
6. The recombinant, recently shaped, plasmids are stirred up with the bacterial cells. Plasmids enter the microscopic organisms in a procedure called transfection. Producers can add to the cell's DNA ligase, a protein that demonstrations like paste to enable the plasmid to adhere to the bacterium's DNA.
7. The microscopic organisms integrating the insulin at that point experience an aging procedure. They are developed at ideal temperatures in huge tanks in assembling plants. The large number of microscopic organisms recreate generally like clockwork through cell mitosis, and every express the insulin quality.
8. In the wake of duplicating, the cells are removed from the tanks and torn open to separate the DNA. One normal way this is done is by first including a blend of lysozome that process the external layer of the cell divider, at that point including a cleanser blend that isolates the greasy cell divider film. The bacterium's DNA is then treated with cyanogen bromide, a reagent that parts protein chains at the methionine buildups. This isolates the insulin chains from whatever remains of the DNA.
9. The two chains are then combined and joined by disulfide bonds through the decrease reoxidation response. An oxidizing operator (a material that causes oxidization or the exchange of an electron) is included. The cluster is then set in a rotator, a mechanical gadget that twists rapidly to isolate cell parts by size and thickness.
10. The DNA blend is then refined so just the insulin chains remain. Producers can cleanse the blend through a few chromatography, or division, systems that endeavor contrasts in the atom's charge, size, and liking to water. Methodology utilized incorporate a particle trade section, invert stage superior fluid chromatography, and a gel filtration chromatography segment. Makers can test insulin bunches to guarantee none of the microscopic organisms' E. coli

proteins are blended in with the insulin. They utilize a marker protein that gives them a chance to distinguish E. coli DNA. They would then be able to confirm that the sanitization procedure expels the E. coli microorganisms.

11. **(Proinsulin Insulin)** Beginning in 1986, makers started to utilize another strategy to incorporate human insulin. They began with the immediate forerunner to the insulin quality, proinsulin. A considerable lot of the means are the same as while delivering insulin with the A and B chains, aside from in this strategy the amino corrosive machine orchestrates the proinsulin quality.
12. The succession that codes for proinsulin is embedded into the non-pathogenic E. coli microscopic organisms. The microscopic organisms experience the aging procedure where it replicates and delivers proinsulin. At that point the associating succession between the A and B chains is grafted away with a compound and the subsequent insulin is cleansed.
13. Toward the finish of the assembling procedure fixings are added to insulin to avoid microscopic organisms and help keep up an impartial harmony amongst acids and bases. Fixings are likewise added to middle and long-acting insulin to deliver the coveted span sort of insulin. This is the conventional strategy for delivering longer-acting insulin. Producers add fixings to the filtered insulin that delay their activities, for example, zinc oxide. These added substances defer retention in the body. Added substances change among various brands of a similar kind of insulin.

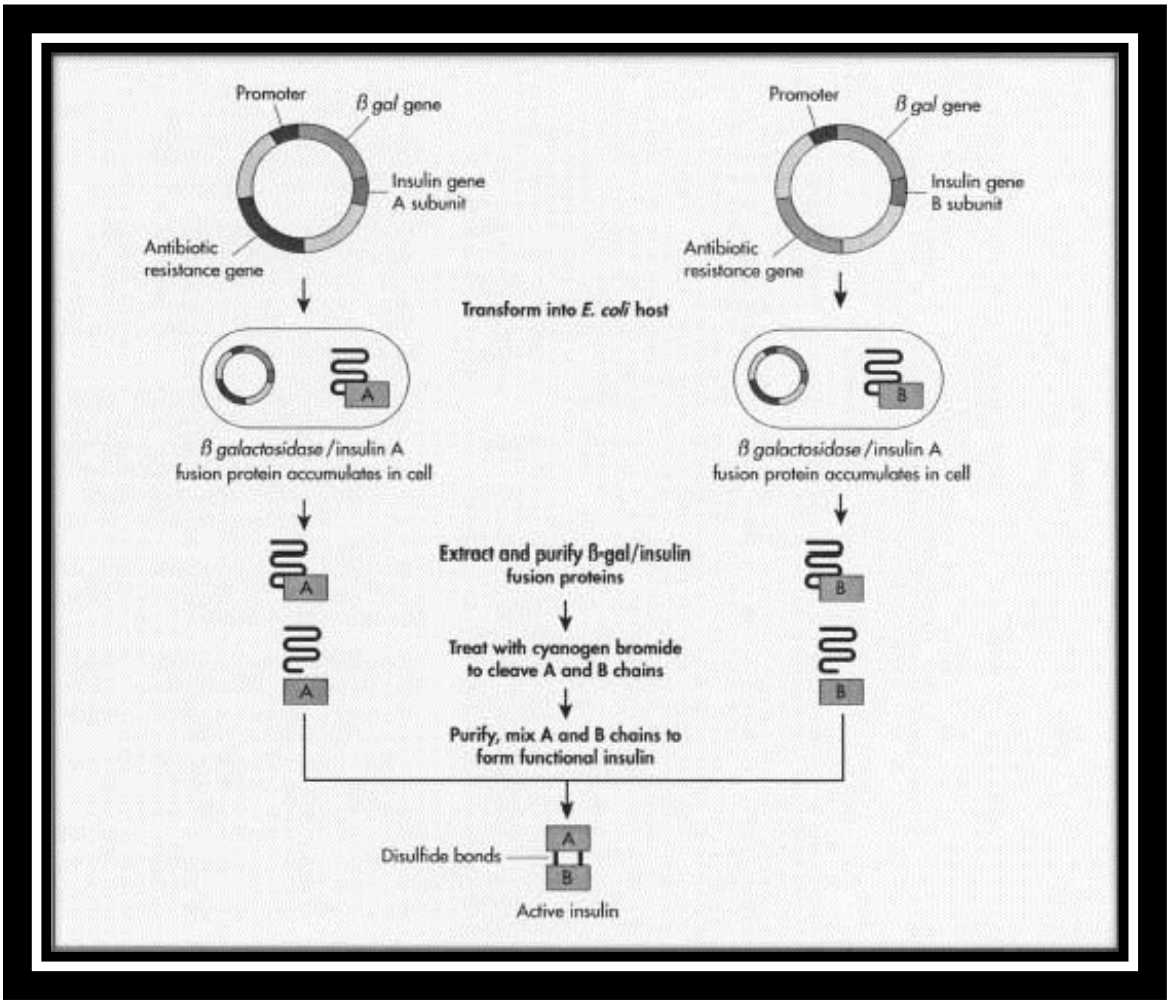

Fig 2: A diagram of the manufacturing steps for Insulin

Quality Control

Subsequent to incorporating the human insulin, the structure and immaculateness of the insulin clumps are tried through a few unique techniques. Superior fluid chromatography is utilized to decide whether there are any pollutions in the insulin. Other partition systems, for example, X-beam crystallography, gel filtration, and amino corrosive sequencing, are additionally performed. Producers additionally test the vial's bundling to guarantee it is fixed appropriately.
Assembling for human insulin must follow National Institutes of Health techniques for substantial scale activities. The United States Food and Drug Administration must affirm all made insulin.

8. Mechanism Action of Insulin

- Insulin follows up on particular receptors situated on the phone layer of for all intents and purposes each cell, yet their thickness relies upon the cell write: liver and fat cells are exceptionally rich.
- The insulin receptor is a receptor tyrosine kinase (RTK) which is a heterotetrameric glycoprotein comprising of 2 extracellular alpha and 2 transmembrane beta subunits connected together by disulfide bonds, situating over the cell film as a heterodimer.

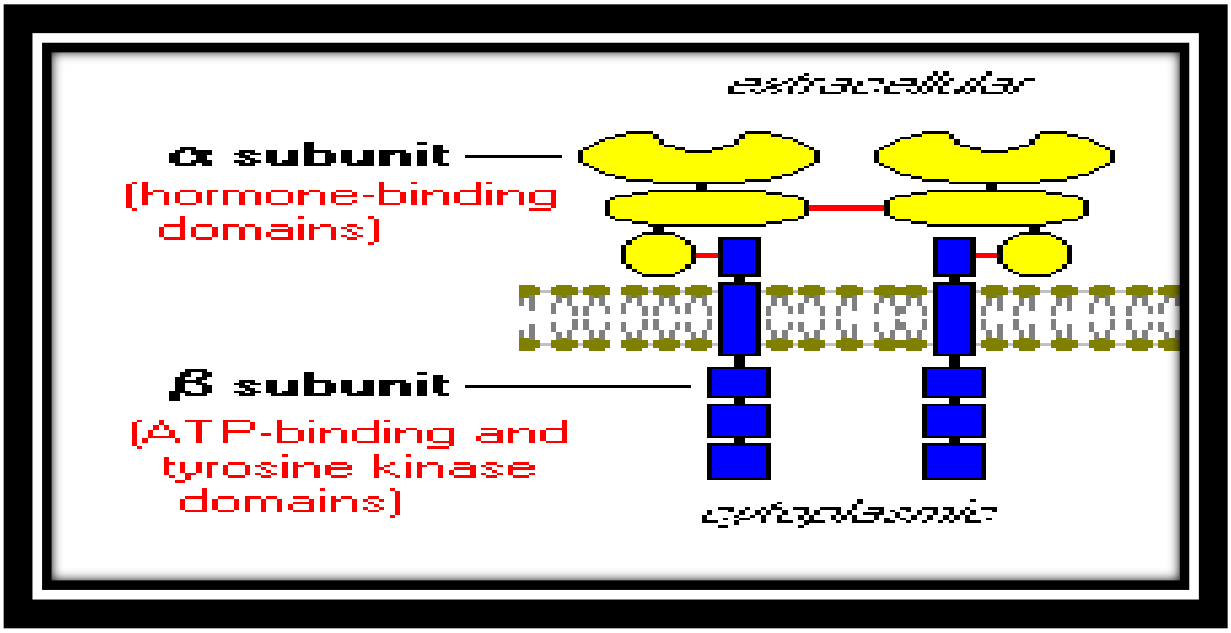

Fig 3: Binding of Insulin

- It is situated over the cell film as a heterodimer.
- The alpha subunits convey insulin restricting locales, while the beta subunits have tyrosine kinase movement.

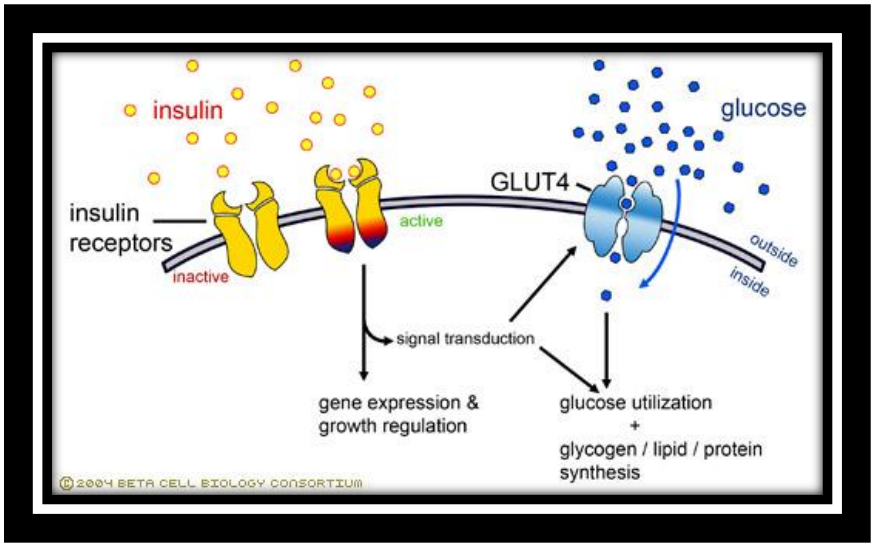

Fig 4: Mechanism of action

- Insulin animates glucose transport crosswise over cell film by ATP subordinate translocation of glucose transporter GLUT4 to the plasma layer.
- The second flag-bearer PIP3 and certain tyrosine phosphorylated guanine nucleotide trade proteins assume urgent parts in the insulin delicate translocation of GLUT4 from cytosol to the plasma layer, particularly in the skeletal muscles and fat tissue.
- Over a timeframe insulin likewise advances articulation of the qualities coordinating union of GLUT4.
- Genes for an expansive number of compounds and transporters are managed by insulin through Ras/Raf and MAP-kinase and through the phosphorylation course.

9. Degradation of Insulin

The disguised receptor-insulin complex is either debased intercellularly or returned back to the surface from where the insulin is discharged extracellularly. The relative dominance of these two procedures varies among various tissues: greatest debasement happens in liver, minimum in vascular endothelium.

10. Way to take insulin in the body

1. Needle and Syringe: With this kind of conveyance framework, you embed a needle into a vial, draw up the proper measure of insulin, and after that infuse into the subcutaneous space—the tissue simply under your skin.
2. Syringe Magnifier: Needle aides can enable you to keep the syringe or pen consistent at the coveted area and at the right point both for drawing up insulin out of the vial and infusing. Some needle manages likewise accompany magnifiers, which help by developing the numbers and permitting to peruse the fine print and measurements on the syringe.
3. Syringe-filling gadget: Syringe-filling gadgets enable a man with diabetes to stack a syringe with a straightforward touch or in some cases to apportion measurements in view of a "tick" sound, and also blend two unique sorts of insulin together.
4. Insulin Pen: This gadget resembles a vast pen that has an insulin-apportioning needle on the end as opposed to ink. Not at all like syringes, insulin pens contain an inherent insulin cartridge that is prefilled with the medication. We turn a dial to the coveted measurements, press a plunger, and infuse the insulin.
5. Jet Injection or Jet Injector: No needle is fundamental with insulin stream injectors, which should settle on them an extraordinary decision for "needle-phobic". Instead, these gadgets utilize high strain to send a fine shower of insulin through the skin.
6. Insulin Pump: These gadgets convey insulin throughout the day. The pump is appended to a little tube or catheter with a needle on the end that is embedded in your skin, more often than not in your guts.

7. Pump Patch: These gadgets are fundamentally insulin pumps that join straightforwardly to the skin; they don't utilize tubing to convey the medication.

11. Selection of Insulin

Porcine insulin is not any more accessible. Cow-like insulin, the most prudent choice for non-bearing patients will be out of market soon, because of natural and ecological contemplations. Human insulin ought to be favored for administration of GDM, diabetic ladies thinking about pregnancy, people with sensitivity or invulnerable protection from creature determined insulins, those starting insulin treatment and those normal to utilize just discontinuously. Changing insulin species and brands ought to be stayed away from as it might influence blood glucose control.

12. Storage and Safety of Insulin

There are some broad principles we ought to take after with regards to the capacity and utilization of insulin:

- Using cool insulin can make your shot more difficult.
- You can warm an insulin bottle by tenderly moving it between your hands previously you fill your syringe.
- If you purchase more than more jug of insulin at once, store the additional container in the fridge until the point when you begin to utilize them.
- Never store insulin at exceptionally cool or exceptionally hot temperatures as outrageous temperatures annihilate insulin.
- Do not put your insulin in the cooler or in coordinate daylight.
- Insulin may lose some strength if the container has been opened for over 30 days.
- Look at the container nearly to make sur the insulin looks 'typical'. For instance, on the off chance that you utilize normal insulin, it ought to be flawlessly clear-no skimming pieces or shading.
- Do not utilize insulin past the lapse date.

13. Mixing of Insulin

Patients who are all around controlled on a specific blended insulin regimen ought to keep up their standard method for setting up their insulin dosages. Insulin glargine ought not to be blended with different types of insulin because of the low pH of its diluent. At present accessible NPH and short acting insulin details when blended might be utilized promptly or put away for sometime later. Quick acting insulin can be blended with NPH, Lente, and ultra Lente. Blending of short-acting and Lente insulins isn't prescribed aside from patients as of now enough controlled on such a blend. On the off chance that short-acting and Lente blends are to be utilized, the patient ought to institutionalize the interim amongst blending and infusion.

14. Timing of injections

Consistent insulin ought to be infused on a normal 30 min before dinners. In the event that quick acting analogs are utilized the time slack ought not to be in excess of 30 min and can be given instantly before or even soon after dinners. Comparable guidelines ought to be given if the patient is utilizing consistent or quick acting insulin blended with different insulins. These interims may should be individualized in a few patients relying upon site of infusion, sort of nourishment, practice and so forth. Transitional acting insulin is best given at sleep time to dodge late night hypoglycemia related with pre supper organization.

15. Sites of taking Insulin

Insulin might be infused into the subcutaneous tissue of the upper arm and the foremost and horizontal parts of the thigh, rear end, and guts (except for a hover with a 2-inch span around the navel). Revolution of the infusion site is vital to anticipate lipohypertrophy or then again lipoatrophy.

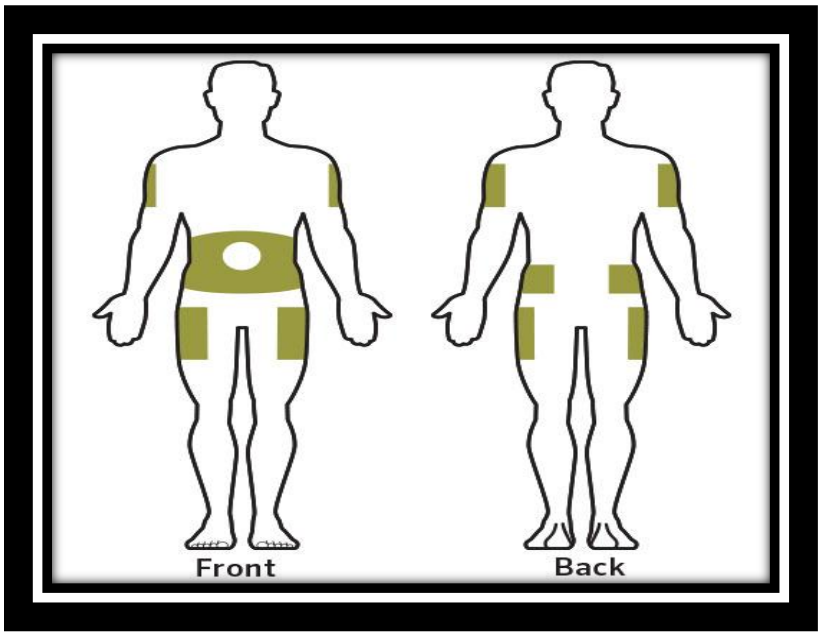

Fig 5: Potential site Insulin Injection

Pivoting inside one region is prescribed (e.g., turning infusions efficiently inside the belly) as opposed to turning to an alternate zone with every infusion. The midriff has the speediest rate of ingestion, trailed by the arms, thighs, and hindquarters. Exercise builds the rate of retention from infusion locales while; zones of lipohypertrophy as a rule indicate slower ingestion. The rate of ingestion is speedier if given intramuscularly and, in spite of the fact that not prescribed for routine utilize, can be given under different conditions (e.g., diabetic ketoacidosis or lack of hydration).

16. Initiating of Insulin

Different regimens are accessible for starting insulin treatment in a diabetic patient. The decision of regimen relies upon the conclusion, glycemic status, quiet agreeable and doctor's decision.

Sliding Scale

Subcutaneous sliding is utilized as a part of a few healing facilities yet isn't prescribed. Sliding scale can be utilized as a part of some circumstance when insulin mixture pump is accessible. 50 U of standard insulin is weakened in 50 ml of ordinary saline and the mixture is begun. Blood glucose should be tried each hour and the rate of mixture is balanced according to clinic glycemic conventions and relying upon the glucose (Sliding scale for IV insulin – Insulin imbuement by means of insulin syringe pump : <120 mg/dl – No insulin; 120 – 200 – 2 U/hr; 200 – 300 – 3U/hr; 300 – 500 – 5U/hr; > 500 – 7U/hr).

Multiple doses

Patient ought to be given 2 dosages of NPH insulin one preceding breakfast (BBF) and one at sleep time and 3 measurements of general insulin 30 minutes before significant dinners. Introductory measurement is begun experimentally and later the dosages are balanced by Self-Monitoring of Blood Glucose (SMBG).

SMBG mirrors the insulin activity as takes after
Fasting – Bed time NPH
Pre-lunch – Regular insulin BBF
Post lunch – consistent insulin before lunch and NPH insulin
BBF
Pre-supper – pre-lunch consistent insulin
Sleep time – pre-supper consistent insulin

Sleep time measurement of insulin can be preponed and blended with predinner dosage of consistent to lessen number of infusions. This may build danger of Somogyi Phenomenon i.e. late night hypoglycemia took after by early morning hyperglycemia.

Split Mixing

Two measurements of insulin with blend of customary and NPH, BBF and predinner are given. Prebreakfast normal insulin should follow up on post breakfast glycemic journey while post lunch crest is relied upon to match with pinnacle of prebreakfast NPH. Thus predinner standard controls the post supper glucose while the predinner NPH follows up on fasting glucose. Measurements are balanced utilizing SMBG.

Bed-time insulin and daytime sulphonylurea (BIDS)

This is utilized as a part of patients going in auxiliary OHA disappointment or if early inception of insulin is considered. One single measurements of NPH is given at sleep time.

17. Factors affecting Insulin Dosage

- Carbohydrate Intake: The more sugar you eat, the more insulin you should take.
- Physical Activity: When we are dynamic, the body expects glucose to fuel our muscles and this can cause blood glucose levels to drop either amid or after exercise. Exercise builds affectability to insulin for up to 48 hours and may require a decrease to insulin dosages.
- Illness: When we are sick, our body will commonly raise our blood glucose levels. Amid times of ailment, we will probably need to take more insulin than expected.
- Body Mass: Typically, the greater you are, the more insulin you will require. Kids with type 2 diabetes, for example, will probably find that their insulin necessities consistently increment as they get more seasoned.
- Insulin Resistance: This is a normal for type 2 diabetes. A bigger protection from insulin will imply that more insulin should be infused to accomplish a lessening in blood glucose levels.

18. Side Effects

- Hypoglycemia: Late night hypoglycemia are for the most part owing to night dosage of middle of the road acting insulin. Moving predinner measurement to sleep time or lessening in sleep time dosage might be required. Postabsorbtive hypoglycemia is generally because of deferred hyperinsulinemia while utilizing short acting normal insulins. It can be avoided by having a tidbit, decreasing measurements of general insulin or substituting with quick acting analogs.
- Weight increase: Initial weight pick up is because of remedy of the catabolic state. Later patient puts on weight by liquid maintenance, and unnecessary eating inferable from hypoglycemia or dread of approaching hypoglycemia.
- Local: Allergy, disease, infusion site sore and lipoatrophy are once in a while observed however lipohypertrophy is as yet normal and is inferable from rehashed infusion of insulin at same site.
- Hypersensitivity: Very seldom observed and requires desensitization with step by step expanding measurements of insulin.

19. CONCLUSIONS

The procedure in pharmacology has brought about the improvement of new insulins with various pharmacokinetic and pharmacodynamics properties. Today every patients with diabetes treated with insulin can be offered individualized treatment coordinating his needs, empowering him to accomplish and keep up great glycemic control and lessening the danger of both constant difficulties and hypoglycemia.

New innovations in tranquilize conveyance frameworks seem promising in that current disagreeable technique for insulin applications may before long progress toward becoming history, and better patient consistence with insulin treatment will be conceivable to accomplish.

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