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Review Article

MODERN APPROCHES OF INSULIN THERAPY: A REVIEW

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ABSTRACT

Some novel drug delivery technologies is increasing now a days. Drug delivery includes several types like oral, transdermal, inhalation and parenteral. The main objective for the delivery of any drug therapy is oral administration with once or twice daily dosing. So there are large numbers of therapies, developed like Growth hormones and other similar biologicals. Now a day's needle-based injections have been developed .for the treatment of diabetes different technologies developed, they are like spray ,pills ,pens, patches, pumps etc**.** These dosage forms are painless and ease of use.
Keywords: CDC- Centre for Disease Control ,WHO-World health organization, QOL- quality of life .

INTRODUCTION

The name insulin comes from the Latin "insula" for "island" from the cells that produce the hormone in the pancreas shown fig no 1. Insulin is a peptide hormone, And like many hormones, insulin is a protein, which is produced by beta cells of the pancreas. Insulin causes cells in the liver, skeletal muscles, and fat tissue to absorb glucose from the blood. Glucose is stored as glycogen, and in fat cells. It is stored as triglycerides. Without insulin, you can eat lots of food and actually be in state of starvation since many of cells cannot access the calories contained in the glucose very well without the action of insulin. This is why people with type 1 diabetes who do not make insulin can became very ill without insulin shots, More commonly ,people develop insulin resistance(type 2 diabetes) rather than a true deficiency of insulin. When control of insulin levels fails, diabetes mellitus can result [1,2].

Insulin chemistry: Insulin produced in the islets of Langerhans in the pancreas. Insulin's structure varies slightly between species of animal. Both porcine (from pigs) and bovine (from cows). Insulin is a protein chain or peptide hormone. There are 51 amino acids in an insulin molecule. It has a molecular weight of 5808 Da [3,4].

Structure of Insulin: Insulin is a small protein, with a molecular weight of about 6000 Daltons. It is composed of two chains held by disulfide bonds shown on fig. no 2[3.4].

Commercial Insulin Comes From: Insulin comes from cows and pigs, the pancreatic islets and insulin protein contained within them were isolated from animals slaughtered for food bovine and procine insulin worked very well for the vast majority of patients, but some could develop allergy or other type of reaction to the foreign proteins [4].

Biosynthesis of insulin: Insulin is synthesized in beta cells in the pancreas. The insulin mRNA is translated as a single chain precursor called preproinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin. Proinsulin consists of three domains: an amino-terminal B chain, a carboxy-terminal A chain and a connecting peptide in the middle known as the C peptide. Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin. Insulin and free C peptide are packaged in the Golgi into secretory granules which accumulate in the cytoplasm. When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuses into islet capillary blood. C peptide is also secreted into blood, but has no known biological activity shown on fig no 3 [3,4].

Release of Insulin: Beta cells in the islets of Langerhans release insulin in two phases. The first phase release is rapidly triggered in response to increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar [3,4].

History:- Discovery & Characterization: In 1869 paul Langerhans ,a medical student of Berlin ,was studying the structure of the pancreas under the microscope .when he identified some previously un-noticed tissue clumps throughout the bulk of pancreas.In 1889,the polish german physician Oscar minikowski in collaboration with joseph von mering removed the pancreas from a healthy dog totest its assumed role in digestion.In 1901 he clearly established the islet of langerhans and diabetis.In 1906 george Ludwig zuelzer was partially successfully treating dogs with pancreatics extract but was unable to continue his work .between 1911-1912E.L.Scott at the university of Chicago ,used aqueous pancreatic extracts ,by Israel kleiner demonstrated similar effects at rockefellar university in 1919,but work wasn't continue due to world war.then in 1921 Nicolae Paulescu ,a professor of physiology at the university of medicine and pharmacy in Bucharest ,was first one to isolate insulin. Then in 1922, Leonard Thompson ,a 14year old diabetic who lay dying at the torrent general hospital, and given the injection of insulin. also best managed to improve his technique to the point where the large quantities of insulin could be extracted on demand. The amino acid structure of insulin was characterized in 1950and first genetically engineered synthetic human insulin was produced in the lab in 1977 by gene tech using E-coli .Eli-lily went on the 1982 to sell first commercially available biosynthetic human insulin under brand name humalin[5].

Disease and syndromes:

1. Diabetes mellitus

They are two types:-

Type 1 Diabetes mellitus

Type 2 Diabetes mellitus

2. Insulinoma

3. Metabolic syndrome

4. Polycystic ovary syndrome[6]

Preparation of Insulin:

Insulin comes in different forms**:**

1. Vials
2. Prefilled syringes
3. Cartridges.

- The Lente human insulin (Novolin L,Humalin L) is available in forms of vials.
- Ultralente Human Insulin (Humanlin U) is available in vials .
- Insulin lispro (humalog) is also available in vials and cartridges
- Insulin aspart (Novolog) is available in vials and cartridges
- Insulin glargine (Lantus) is available in vials and cartridges [6].

STORAGE: Insulin can be stored in a refrigerator between 2-8^{o}c .it should not be placed in a freezer. Insulin vials can be kept in a room temperature for upto a month. All vials should be protected from light and excessive heat. unused insulin should be thrown away after the expiration date. vials should never be shaken [6].

PRESCRIBED FOR: For treatment of type 1 and type 2 diabetes mellitus [6].

Insulin Therapy: Insulin therapy is the treatment of diabetes by administration of exogenous insulin. Insulin is used medically to treat some forms of diabetes mellitus. Patients with Type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with Type 2 diabetes mellitus are insulin resistant, have relatively low insulin production, or both; certain patients with Type 2 diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately.

Modern Approches of Insulin Therapy: Doctor and patients having hope for an alternative to insulin injection .many advance have been made to make injecting insulin with needleless uncomfortable by using different technique such as pumps and pens. They are given below:-

1. Insulin pens
2. Insulin inhalers
3. Insulin pills
4. Implantable insulin pump
5. Debiotech
6. Eksigent's pump
7. Jet injectors
8. Jet injectors gun

Insulin pens: The basal /bolus approach for matching insulin to need to require convenient , precise way to take doses of insulin anytime anywhere [7].

Insulin inhalers: In September 2006 – October 2007 in the U.S as a new method of delivering insulin, a drug used in the treatment of diabetes to the body. **Exubera**, a powdered form of recombinant human insulin, delivered through an inhaler into the lungs where it is absorbed. Insulin has also been known to help patients with breast cancer, namely women. Once it has been absorbed, it works within the body over the next few hours. Type 1 diabetics still need to take a longer acting basal insulin by injection.

Exubera is considered a short or rapid acting insulin. In clinical studies, Exubera reached peak concentration levels faster than some insulins administered by injection. Thus, this form of insulin would begin working within the body faster than those forms of injected insulin. Type 1 and 2 diabetics will still need an injection of longer acting insulin to maintain a basal level for a 24 hour period [8,9].

Insulin pills: The discovery of new polymer that may allow development of an effective insulin pill was reported at a recent meeting of the American chemical society. When a polymer is used as a pill coating , it allows to get into the bloodstream without being destroyed by the digestive system .so far it has only been tested in the animals .oral insulin has been a possibility for a long time but dealing with the breakdown caused by digestive juice were shown on fig no 4.

Implantable insulin pump: Though the skin is a formidable barrier, companies are developing various active transdermal delivery technologies to overcome this challenge. The hope is to open up the transdermal market to the delivery of products that were previously considered undeliverable via this route [7,8].

Insulin pump: The insulin pump is a medical device used for the administration of insulin in the treatment of diabetes mellitus, also known as continous subcuataneous insulin infusion therapy and shown on figure no 5. The device include

- The pump (including controls, processing module, and batteries)
- A disposable reservoir for insulin (inside the pump)
- A disposable infusion set, including a cannula for subcutaneous insertion (under the skin) and a tubing system to interface the insulin reservoir to the cannula[7,8].

Insulin pump Dose:-

The insulin pump delivers a single type of rapid-acting insulin in two ways

- A bolus dose that is pumped to cover food eaten or to correct a high blood glucose level.
- a basal dose that is pumped continuously at an adjustable basal rate to deliver insulin needed between meals and at night

Advantages of Insulin pump:

- Pumpers report better quality of life (QOL) compared to using other devices for administering insulin. The improvement in QOL is reported in type 1 and insulin-requiring type 2 diabetes subjects on pumps.
- The use of rapid-acting insulin for basal needs offers relative freedom from a structured meal and exercise regime previously needed to control blood sugar with slow-acting insulin.
- Programmable basal rates allow for scheduled insulin deliveries of varying amounts at different times of the day. This is especially useful in controlling events such as Dawn phenomenon.
- Many pumpers feel that bolusing insulin from a pump is more convenient and discreet than injection.
- Insulin pumps make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar and Hemoglobin A1c levels, reducing the chance of long-term complications associated with diabetes. This is predicted to result in a long-term cost savings relative to multiple daily injections.
- Many modern "smart" pumps have a "bolus wizard" that calculates how much bolus insulin you need taking into account your expected carbohydrate intake, blood sugar level, and still-active insulin.
- Insulin pumps can provide an accurate record of insulin usage through their history menus. On many insulin pumps, this history can be uploaded to a computer and graphed for trend analysis.
- Neuropathy is a troublesome complication of diabetes resistant to usual treatment. There are reports of alleviation or even total disappearance of resistant neuropathic pain with the use of insulin pumps.
- Recent studies of use of insulin pumps in Type 2 diabetes have shown profound improvements in HbA1c, sexual performance, and neuropathy pain.

Disadvantages of insulin pump:-

- Insulin pumps, cartridges, and infusion sets are far more expensive than syringes used for insulin injection.
- Since the insulin pump needs to be worn most of the time, pump users need strategies to participate in activities that may damage the pump, such as rough sports and activities in the water. Some users may find that wearing the pump all the time (together with the infusion set tubing) is uncomfortable or unwieldy.
- An episode of diabetic ketoacidosis may occur if the pump user does not receive sufficient fast acting insulin for many hours. This can happen if the pump battery is discharged, if the insulin reservoir runs empty, the tubing becomes loose and insulin leaks rather than being injected, or if the cannula becomes bent or kinked in the body, preventing delivery. Therefore pump users typically monitor their blood sugars more frequently to evaluate the effectiveness of insulin delivery.
- Possibility of insulin pump malfunctioning, and having to resort back to multiple daily injections until a replacement becomes available. However most pump manufacturers will usually have a program that will get a new pump to the user within 24 hours or allow the user to buy a second pump as a backup for a small fee. Additionally the pump itself will make many safety checks throughout the day, in some cases up to 4,000,000 and may have a second microprocessor dedicated to this.
- Users may experience scar tissue buildup around the inserted cannula, resulting in a hard bump under the skin after the cannula is removed. The scar tissue does not heal particularly fast, so years of wearing the pump and changing the infusion site will cause the user to start running out of viable "spots" to wear the pump. In addition, the areas with scar tissue buildup generally have lower insulin sensitivity and may affect basal rates and bolus amounts. In some extreme cases the insulin delivery will appear to have no/little effect on lowering blood glucose levels and the site must be changed.
- Users may experience allergic reactions and other skin irritation from the adhesive on the back of an infusion set. Experience may vary according to the individual, the pump manufacturer, and the type of infusion set used.
- A larger supply of insulin may be required in order to use the pump. Many units of insulin can be "wasted" while refilling the pump's reservoir or changing an infusion site. This may affect prescription and dosage information.

DRUG DELIVERY SYSTEM OF INSULIN PUMP

Insulin pumps deliver rapid- or short-acting insulin 24 hours a day through a catheter placed under the skin. Your insulin doses are separated into:

- Basal rates
- Bolus doses to cover carbohydrate in meals
- Correction or supplemental doses

Basal insulin is delivered continuously over 24 hours, and keeps your blood glucose levels in range between meals and overnight. Often, you program different amounts of insulin at different times of the day and night.

When you eat, you use buttons on the insulin pump to give additional insulin called a bolus. You take a bolus to cover the carbohydrate in each meal or snack. If you eat more than you planned, you can simply program a larger bolus of insulin to cover it.You also take a bolus to treat high blood glucose levels. If you have high blood glucose levels before you eat, you give a correction or supplemental bolus of insulin to bring it back to your target range.Knowing how an insulin pump works is one thing. But you may be wondering where you are supposed to put it. You can buy a pump case or it can be attached to a waistband, pocket, bra, garter belt, sock, or underwear. You can also tuck any excess tubing into the waistband of your underwear or pants.When you sleep, you could try laying the pump next to you on the bed. You could even try wearing it on a waistband, armband, legband, or clip it to the blanket, sheet, pajamas, stuffed toy, or pillow with a belt clip.Showering and bathing are other instances when you should know where to put your insulin pump. Although insulin pumps are water resistant, they should not be set directly in the water. Instead, you can disconnect it. All insulin pumps have a disconnect port for activities, such as swimming, bathing, or showering. Some pumps can be placed on the side of the tub, in a shower caddy, or in a soap tray. There are also special cases you can buy. You can hang these cases from your neck or from a shower curtain hook.No matter what you may think, you can still have fun when you are using an insulin pump. When you exercise or play sports, you can wear a strong elastic waist band with a pump case. You can also wear it on an armband where it is visible. Women can tape the insulin pump to the front of their sports bra. Some coaches do not allow any devices to be worn because getting the pump knocked into you or falling on it can be painful. In this case, you may just need to take the insulin pump off.When you disconnect your pump, you are stopping all delivery (basal and bolus) by the pump. Here are some important tips to remember when disconnecting your pump.

1. It is important for you to remember that if you stop your pump while it is in the middle of delivering any bolus -- it will NOT be resumed. You may need to program a new one.
2. Be sure to bolus to cover the basal rate you will miss. If your blood glucose level is under 150, you can wait an hour to bolus.
3. Do not go longer than one to two hours without any insulin.
4. Monitor your blood glucose every three to four hours.

Technique of apply pump

Insulin pump has following steps are shown on fig no 6:-

1. Sterile technique
2. Insulin and dressing
3. Infusion sets
4. Infusion sites
5. Site sterilization[7,8].

Debiotech Pump Debiotech: developed by swiss team with French/Italian from the manufacturer STMicroelectronics to bring to market a miniaturized insulin pump. The Nanopump, which relies on microfluidic MEMS (Micro-Electro-Mechanical System) technology, is a breakthrough concept that allows a tiny pump to be mounted on a disposable skin patch to provide continuous insulin infusion. The Nanopump will enable substantial advancements in the availability, treatment efficiency and the quality of life of diabetes patients. The original technology was awarded the Swiss Technology Award in 2006 and this agreement brings it closer to the market. Insulin pump therapy, or Continuous Subcutaneous Insulin Infusion (CSII), is an increasingly attractive alternative to individual insulin injections that must be administered several times a day. With CSII, the patient is connected to a programmable pump attached to a storage reservoir, from which insulin is infused into the tissue under the skin. Continuous delivery throughout the day, more closely mimics the natural secretion of insulin from the pancreas. The highly miniaturized disposable insulin pump combines Debiotech's expertise in insulin delivery with ST's strengths in manufacturing high-volume silicon-based microfluidic devices. Microfluidic technology allows the flow of very small amounts of fluids to be electronically controlled. This pump represents a significant step in the development and adoption of CSII therapy and the leading-edge technology will also find applications in many other biomedical applications. The new ST-enabled Debiotech miniaturized MEMS device is about one quarter the size of these existing pumps and can be worn as a nearly invisible patch on the skin. The small size frees the patient from concerns with holding the pump in place and concealing it under clothing. The MEMS-based Nanopump also provides better control of the administered insulin doses. Dosing precision is a critical factor in treatment efficacy and contributes to reducing adverse long-term consequences. The Nanopump is able to control delivery at the nanoliter level, very close to the physiological delivery of insulin. The device prevents over-dosing and detects under-delivery, occlusion, air bubbles and other potential malfunctions in the pump to further protect patients. As a disposable device, manufactured using high-volume semiconductor processing technologies, the MEMS-based Nanopump will also be much more affordable, allowing the patient or the health system to avoid the typical up-front investment associated with current pump solutions. The insulin Nanopump, developed by Debiotech and industrialized by ST, represents the first use of microfluidic MEMS technology in diabetes treatment and shown on fig no 7

Transdermal insulin: The skin play a primary roles is to provide protection against infection and physical damage. This barrier is so effective that it prevents many pharmaceutical compounds from crossing into the bloodstream. To overcome this , both passive and active drug transport across the skin barrier are being developed.Passive transdermal delivery allows a drug to diffuse through the skin and act locally or penetrate the capillaries and have a systemic effect. Passive delivery usually occurs with a patch, cream, or spray. Passive Transdermal delivery only works with small molecule drugs, such as nicotine and aspirin. Insulin is far too large to get through the skin passively.Active transdermal delivery, on the other hand, involves a chemical or mechanical disruption of the skin barrier. By using an applied force, such as ultrasound or an electrical current, active transdermal systems are capable of delivering proteins and other large molecule formulations through the skin and into the bloodstream and it shown on fig no 8[12].

EKSIGENT 'S PUMP

It is design for drug delivery of insulin. it is suited for micropumping application.

1. It is small in size
2. Flexible
3. Ease of use

Features:

1. Small light weight ,in expensive,disposable for inconspicuous attachment.
2. No moving parts,easy integration into device
3. Completely programmable for dosage levels,operating on a watch battery
4. Flow rate=2-5%

Configuration

1. Low capacity-1 week
2. Medium capacity-1 month
3. High capacity-3 month

Pump Kits:

1. Filling kit
2. Materials test kit

Jet injectors:

A jet injector is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis. It is powered by compressed air or gas, either by a pressure hose from a large cylinder, or from a built-in gas cartridge or small cylinder. Some are multi-shot, and some are one-shot. They are used by diabetics to inject insulin as an alternative to needle syringes, though they are still not very common.

Types of jet injector:

1. **Jet Injectors Gun**
2. **Biojector 2000**

Jet Injectors Gun:

The Jet Injector Gun Ped-O-Jet is air-powered medical injector devices designed to administer vaccinations in an extremely efficient manner. Invented by Aaron Ismach. The Jet Injector is powered by electricity, while the Ped-O-Jet version is powered by a foot pump and does not require electricity to administer the vaccines. These devices have various specialized nozzles for different medication densities and also permitted the efficient inoculation of animal populations as well. Care must be taken around high pressure sprays of this kind to avoid such injuries.

Biojector 2000:

The Biojector 2000 is an new drug delivery system with an innovative, versatile needle-free injection system that has been used to deliver millions of injections in a wide range of healthcare settings. The Biojector has different features, including deliver both intramuscular and subcutaneous injections up to 1 ml in volume. In 1993, the Biojector has set a new standard for the comfort, safety, and convenience of injection equipment. The Biojector has FDA clearance for delivering subcutaneous or intramuscular injections of liquid medication, including vaccines and other injected medications. Because there is no needle, the Biojector provides healthcare workers with an unparalleled level of protection against accidental needlestick injuries. In high-risk situations, such as delivering injections to patients known to be infected with HIV or Hepatitis, the Biojector is an ideal injection system.The Biojector works by the same principle as all of Bioject's needle-free injection systems: by forcing liquid medication through a tiny orifice that is held against the skin. This creates a very fine, high-pressure stream of medication that penetrates the skin, depositing medication in the tissue beneath. The system has three components: a durable injection device, a disposable needle-free syringe, and a CO2 cartridge. Needle-free technology offers the very obvious benefit of reducing patient concern about the use of needle. Additional benefits include very fast injection compared with conventional needle and no needle disposal issues. Not only it can benefit the pharmaceutical industry in increasing product sales, it has the added potential to increase compliance with dosage regimens and improved outcomes. In the developing world, there are major challenges of disease transmission through re-use of needles. Organisations such as WHO and CDC (Centre for Disease Control) and groups like Gates Foundation have supported the development of needle-free alternatives for drug delivery.

CONCLUSION

By using an insulin pump you can match your insulin to your lifestyle ,rather than getting an insulin injection and matching your life ,insulin pump can help you keep your blood glucose levels within your target range .spray have low viscosity provided greater surface coverage of mucosa than higher viscosity formulations. Changes in the breathing profile did not affect the aerosol deposition in this mode, further more formulation developed for give better response.

REFERENCES

1. 1.Bell GI, Pictet RL,Rutter WJ, Cordell B,Tischer E,Goodman HM.”sequence of the human insulin gene”,Nature 284:26-32
2. Koda-Kimble MA, Young LY, Kradjan WA, Joseph B, Allodredge BK ; Diabetes Mellitus ; In: Applied Therapeutics- The clinical use of drug, Philapedia, Corelli Lippincott and Willkins:2004 ;13,50.
3. 3 .Murray I.”paulesco and the isolation of insulin ”.journal of the history of the medicine and allied science26(2):150-157
4. Ledd JJ .”Solution structures of the R6 human insulin hexamer ”.biochemistry 36:409-422
5. http://en.wikipedia.org/wiki/insulin.
6. Verge D. Insulin: New molecules and routes of administration-Biotechnological innovations in insulin therapy, Medical Science 2004, 20, 986-998.
7. 7.wikipedia.org/wiki/insulin-pen
8. 8.wikipedia.org/wiki/insulin-therapy_inhaler.
9. 9.wikipedia.org/wiki/insulin-spray
10. en.wikipedia.org/wiki/jet_injector.
11. http://infoscience.epfl.ch/record/173357
12. http://en.wikipedia.org/wiki/Transdermal_patch

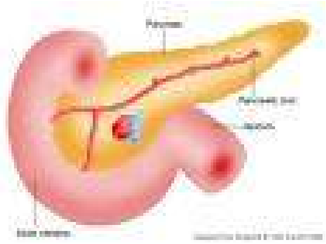

Figure 1: Pancreas

b

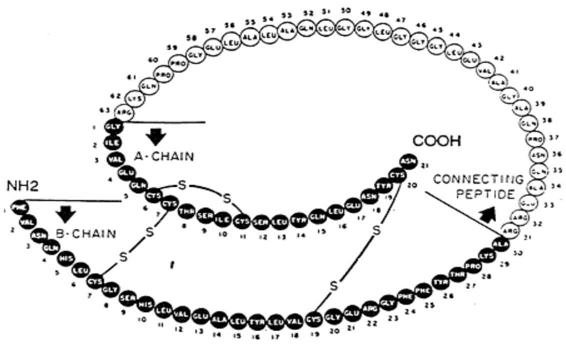

Figure 2: Structure of Insulin

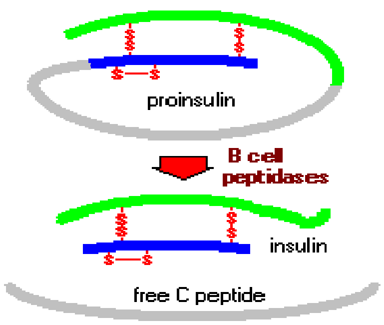

Figure 3: Biosynthesis of insulin

Figure 4: Insulin Pills

Figure 5: Insulin Pump

Figure 6: Insulin Spray

Figure 7: Debiotech Pump

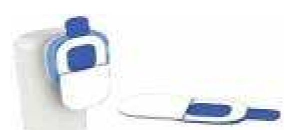

Figure 8: transdermal insulin patches

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