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Overview of insulin pump therapy in type 1 diabetes

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Abstract

Diabetes is a fast growing epidemic in most parts of the world. Type 1 diabetic patients and some Type 2 Diabetic patients require insulin for better diabetes management. Insulin pump treatment also called Continuous Subcutaneous Infusion therapy is a better and efficient insulin delivery method as compared to multiple injection regimen. With advancement in technology, more adaptable and lifestyle friendly pumps have developed which provide an effective Insulin delivery to the patients along with glucose monitoring. The article aims to give an overview of Insulin pumps therapy, its market and future. With the number of Diabetic patients increasing worldwide and advancement in technology of insulin pumps with time, the demand of insulin pump is overgrowing.

Keywords: pump therapy, type 1 diabetic, type 2 diabetic patients

Introduction

The condition where the body is not able to produce enough insulin or is not able to utilise the insulin produced in the body, is called Diabetes. Insulin is a hormone that controls the amount of glucose (sugar) in the blood. It is created in the pancreas and is considered the "most powerful" hormone in the body.

When blood sugar levels in a healthy person exceed normal blood sugar level, pancreas release insulin. Insulin causes cells to take in sugar and use it as energy or to store fat which helps in obtaining normal blood sugar level.

Types of Diabetes

- **Type 1 Diabetes:** In this category, no or very less insulin is released into the body. The exact cause of Type 1 is not yet known, but we do know it has a family link and cannot be prevented. We also know that it has nothing to do with lifestyle, although maintaining a healthy one is very important for better management

Symptoms include blurred vision, passing more urine, unexplained weight loss and mood swings.

- **Type 2 Diabetes:** In this category, the body is not able to utilise the insulin produced. This type runs in the family, while people may have a strong genetic disposition towards it, the risk is higher if people display some modifiable lifestyle factors including high blood pressure, obesity, poor diet.

Symptoms of type 1 diabetes are similar, but often less marked.

For people suffering from diabetes, they have to externally take insulin depending on the need of the human body. The University of California, San Francisco explains that insulin "was initially extracted from beef and pork pancreas. In the early 1980's, technology became available to produce human insulin synthetically. Synthetic human insulin has replaced beef and pork insulin in the US. And now, insulin analogs are replacing human insulin."

The chart below tells about the types of insulin.

Insulin is externally taken either in the form of a tablet or with the help of a syringe. With the evolution of technology insulin now can be administered with the support of a pump.

Insulin pumps: As the name suggests it is a device that helps to deliver insulin to the people who are suffering from diabetes. It is a small battery operated device approximately equivalent to the size of a cell phone. It is connected to a narrow plastic tube that is inserted just under the skin and taped in place. Insulin pumps precisely deliver doses of rapid-acting insulin to match the needs of a human body closely.

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- **Basal Rate:** Small amounts of insulin delivered continuously for normal functions of the body (not including food). The programmed rate is determined by the professional.
- **Bolus Dose:** Additional insulin which is delivered "on

demand" to match with the food eat or to correct a high blood sugar.

Insulin pumps have bolus calculators that help you calculate your bolus based on settings that are determined by the healthcare professional.

Type of Insulin	Brand(Generic)	Onset	Peak	Duration
Rapid-Acting	Apidra(glulisine),Humalog (lispro), Novolog(Aspart)	15 minutes	1 or 2 hours	2 to 4 hours
Regular-or-Short -Acting	Humulin R, Novolin R(human recombinant)	30 minutes	2 to 3 hours	3 to 6 hours
Intermediate-Acting	Humulin N, Novolin N(insulin isophane)	2 to 4 hours	4 to 12 hours	12 to 18 hours
Long-Acting or Basal Insulin	Lantus(glargine), Levemir(detemir), Basalgar(glargine)	2 to 4 hours	Lower peak	24 hours
UltraLong-Acting	Toujeo(glargine), Tresiba(degludec)	6 hours	Small peak	36 hours
Inhaled Insulin	Afrezza(insulin human)	15 minutes	30 minutes	3 hours

Working of insulin pumps

The insulin pump is attached on the outside of the body. Insulin is delivered through a tube (catheter), which is connected to a thin cannula, placed under the layer of fat of the skin, mostly around the stomach area. To use an insulin pump, the person will need hands-on training from the healthcare professionals. The patient must know how to fill a pump reservoir, select an infusion site, change an infusion set, disconnect the device, calculate and program basal and bolus doses, troubleshoot potential problems, prevent diabetic ketoacidosis and create backup plans in case of pump failure diabetic ketoacidosis.

Types of insulin pumps

There are many Insulin pumps available on the market. Tethered and patch pumps are the options currently available to buy privately. Currently, closed-loop insulin pumps are being tested, whereas very less population uses implantable insulin pumps.

1. Tethered Pump: These pumps have a length of flexible tubing between the pump itself and the cannula. The pump itself, which usually feature controls, can be freely tucked into pockets or can be worn under or outside of clothing.

Commonly available tethered pumps are Medtronic MiniMed paradigm Veo Accu-Chek spirit combo, Animas Vibe.

2. Patch Pump: A patch pump is attached to the surface of the skin. The pump is controlled by the remote control which may also be a blood glucose meter. Patch pump is different in the fact that there's no tubing to attach on handles and other such objects

Example: The mylife Omni Pod patch pump is available in UK, France, Switzerland etc.

- **Implanted insulin pump (IIP):** An implanted insulin pump is a pump which is attached inside the patient's body via surgery. An implanted insulin pump delivers insulin into the peritoneal cavity which has a plentiful supply of blood vessels and hence absorption of insulin is very efficient.

The implantable insulin pump therapy came into existence around 1980, when insulin pump was first implanted in a diabetic patient as an experiment at the University of Minnesota in Minneapolis. In 2000s Minimed came up with an implantable insulin pump which is used till date. Not much modification is observed since then in the pumps.

Decidedly lesser population around the world uses implanted insulin pumps

- **Closed Loop insulin pump:** Closed-loop insulin pumps, also referred as an 'artificial pancreas', are pumps which can respond automatically to readings given by a continuous glucose monitor which also needs to be worn by the user through each day. A comprehensive set of rules and algorithms are required to respond to changes in blood glucose levels and ensure blood glucose levels stay within safe levels, and to date, these pumps are still in the research stage of development.

Currently, these pumps are under the research stage of development.

Evolution of insulin pumps

In the absence of insulin pump, diabetic patients had to conform to a rigid diet with particular emphasis on the low amount of carbohydrates and calories, which had severe repercussions on the individual's health.

Introduction of the insulin pump, which has been circulating for 30 years now, has helped in improving the lives of diabetic patients. It has wholly terminated the multiple injections regime due to its efficiency and quickness. Insulin pump therapy gives patients more flexibility and freedom to perform its day to day tasks and ease the demands of diabetes management.

A quick overview of advancement of insulin pumps technology throughout the years:

- **1963:** Dr Arnold Kadish developed the first prototype for a pump Kadish. The closed-loop insulin pump device that he designed worked by providing continuous insulin to the body combined with continuous glucose sensing. It comprised a large pump with an auto analyser, which was operated to measure blood sugar with an on-off servo-mechanism that controlled the pump function when blood sugar was out of the normal blood sugar ranges.

The major drawback of this device was that size of the device was equal to a microwave and was supposed to be worn as a backpack.

- **1973:** The first wearable infusion pump was invented by Dean Kamen while studying physics at Worcester Polytechnic Institute (WPI). The device was used for chemotherapy and endocrinology and was transformed into the first wearable insulin pump for diabetic patients later.

- **1976:** The first wearable insulin pump which was designed from Dean Kamen's 1973 invention, commenced to be manufactured and marketed for public use.

The same year, in 1976, Continuous Subcutaneous Insulin Infusion, also known as insulin pump therapy was introduced.

- **1980:** A controlled insulin infusion system was developed that acted as artificial system. Again, in 1980, an implantable pump was created, and testing began on humans.
- **1982:** The first insulin pump was developed which could programme individual's basal rate.
- **1986:** The implantable pump was implanted in the patient who was not a test subject.
- **2003:** The first pump that could monitor blood glucose levels was created.
- **2012:** Trials for artificial pancreas began in the United States
- **2015:** First touchscreen insulin pump was released into the market which also had continuous glucose monitoring feature and delivered insulin in increments as small as 0.001u/hr and at rates about 0.1u/h.

The 1990s period portrayed a new era in the establishment of insulin infusion pumps. Production of more functional pumps with safety measures began with the time that gave alarms and alerts for problems such as infusion set occlusion, as well as a 'low' battery or low insulin reservoir.

Today, many options are available for the patients and clinicians to choose from. Pumps as small as pagers are also produced which boast of extended battery life and enhanced safety measures and reduce the problem of site infection with the help of plastic catheter infusion sets. Even the pumps are now made more aesthetically pleasing as well as user-friendly with different colours and large displays.

The latest ones also allow patients to program several different basal rates to be used in one day to accommodate diurnal changes in insulin needs. They calculate bolus doses as well as basal doses. Smart pumps have inbuilt dosage calculators to perform an automatic estimation of active insulin remaining from the previous bolus, and predict the amount of insulin that should be administered based on several factors, those being blood glucose concentration and anticipated amount of ingested food.

Some pumps also offer the ability to change the shape and duration of the boluses to cater to the variable needs of insulin based on lifestyle as more advanced treatment strategies. A 'square wave' bolus mode is used to deliver a single bolus dose of insulin over an extended period, while a 'dual wave' bolus mode is used to deliver two boluses; one immediately and another within a few hours later.

Current insulin pump devices

Currently, there are seven manufacturers supplying insulin pumps worldwide:

- Medtronic MiniMed
- Roche's Disetronic Medical Systems
- Animas (Johnson & Johnson)
- Deltec (Smiths Group)
- Sooil, Nipro
- Insulet Cooperation Ltd.

Medtronic MiniMed is the market leader for insulin pumps (Paradigm pumps) in the US, having approximately 85% market share (44). Roche's Disetronic is the market leader outside the US, with about 15% market share (36). Until 2000, Medtronic MiniMed and Disetronic had the monopoly over the pump market while Animas had its launch in 2001. Sooil and Nipro manufacture devices for continuous subcutaneous insulin delivery; being Dana Diabecare Pumps and Amigo Pumps, respectively.

The latest manufacturer of insulin pumps is Insulet which produces OmniPod disposable insulin pumps, which received FDA approval in January 2005.

Roche's Disetronic Medical Systems initially marketed the only pump available in the UK.

Starbridge System Ltd is a UK-based medical company that was established in March 2002. The company has developed a new generation insulin pump, Starlet Pumps, which operate via laser-heated wax to drive a minute pump and valves to supply insulin. This system can be worn as a patch on patients' skin to provide a 24-h supply of insulin. Starlet pumps represent smaller and lighter alternatives to current insulin pumps while maintaining the same level of diabetes control. However, this pump is still under development and the time frame for its entry.

Market analysis of insulin pumps

The global insulin pumps market is estimated to witness a CAGR of 8.3% during the forecast period 2017–2023. Increasing awareness about diabetes and glucose monitoring devices has a significant impact on the insulin pump market growth.

Product Analysis: Advanced insulin pumps such as Medtronic's MiniMed 530G system are emerging in the market. In developed countries, knowledge about the advantages of insulin pumps systems over traditional injections, and glucose monitors has led to the increase in market growth.

Regional Analysis: The Americas is set to be the leading region for the insulin pumps market growth followed by Europe. The Asia Pacific and ROW are the emerging regions for insulin pump market. The markets in India, Brazil, and China are growing at a rapid pace as the prevalence of diabetes and other lifestyle diseases in these countries is high.

Key Players: Animas is the leader in the insulin pumps market. Medtronic, Asante, Roche, Cellnovo, and Insulet are the other major players in the insulin pump market.

Competitive Analysis: The tethered pumps dominate the global insulin pumps market. The future of the market is expected to be influenced by the advanced products such as MiniMed 530G system and OmniPod insulin pumps. The large players such as F. Hoffmann-La Roche and Medtronic are acquiring companies with products that would complement their existing portfolio. Significant investments in R&D in this market are expected to increase, and collaborations and M&A are expected to continue.

The key factors responsible for increasing market of Insulin Pump are the increase in the number of diabetic patients, advancement in technology, improved glucose control and flexibility. However, high cost of the insulin pump devices is anticipated to influence the growth of the market in future. Insulin pumps cost in the range of \$2500-\$6500 USD, and its accessories cost around \$100 per month. In developed countries like the United States, European Union etc. private insurance companies give insurance on insulin pumps due to which more significant number of diabetic population can afford insulin pumps. It has been reported that around 50% of diabetic patients in the United States and 25% of diabetic patients in European Union countries are pump users. However, in developing countries such as India, the number

of pump users are lesser comparatively, around 5-7% of total diabetic patients because of its high cost and absence of insurance coverage. Lack of knowledge, lower availability of pumps as compared to USA and EU are some other factors influencing the insulin pump market in developing countries.

Future Directions

The future of insulin pump therapy is optimistic. Currently, all insulin pumps are based on an open-loop insulin infusion system, where the insulin delivery rate is not automatically adjusted according to the blood glucose levels. The patient has to decide on the basal insulin infusion rate throughout the day and calculate boluses to be administered before each meal. This makes the process of diabetes control difficult, stressful, and open to non-optimal dosing especially in the night and in cases of paediatric patients.

The closed-loop system, on the other hand, will allow real-time communication between an infusion pump and a glucose sensor. The system will be able to sample, filter and interpret the data of glucose sensor, will be able to compare blood glucose samples according to the target readings, and precisely calculate and adjust insulin doses to maintain normal glycaemia level. Furthermore, the closed-loop system will be able to react to variations in measured glucose level and respond quickly to fulfil insulin needs and be capable of recognising and correcting spurious readings. For example, if blood glucose concentrations will exceed normal standards, the closed-loop operated pumps will increase delivery of insulin when blood glucose concentrations go below normal levels, the pump will either interrupt or reduce insulin delivery, and when necessary inject counter-regulatory hormones such as glucagon. The insulin pump and glucose sensor would in effect serve as an artificial pancreas by operating together in a closed-loop system. They would imitate the pancreatic beta cells' action and which would be an advantage to the diabetic patients as they will not have to deal with tedious continuous blood glucose monitoring and adjustments of food intake, and calculation of insulin doses, which is done currently with open-loop pumps.

FDA has approved MiniMed 670G Insulin Pump System which is produced by Medtronic in September 2016. The insulin pump consists of two parts, the MiniMed 670G pump and the Guardian Sensor 3 to monitor glucose levels. This pump is developed for Type 1 diabetic individuals only

Other competitors in the Closed loop system market are Cellnovo, Diabeloop, Dexacom, Tandem Diabetes, Bigfoot biomedical and Abbott. Their artificial pancreas is currently under trials and expected to be launched soon.

Conclusion

Insulin pump therapy is gaining popularity as an insulin replacement method for diabetic patients. In developed countries, such as the United States, insulin pumps are used commonly, and in India and other developing countries, insulin pump market is increasing at a faster rate. The advantage of CSII over other insulin delivery methods is the flexible and easily adaptable lifestyle. Insulin pumps have been in the market for more than 30 years now, from a microwave-size pump to small pager-sized devices that can monitor the blood glucose level and dose the correct amounts automatically. The insulin pump market is expected to grow at faster rate in the upcoming years despite the high cost. Medtronic is the leading company in the market efficiently controlling most of the shares, whereas other core Insulin

companies such as Lilly, Novo Nordisk and Sanofi are expected to take a step ahead by entering the insulin pump market. The artificial pancreas is the future of Insulin pump treatment which will provide more freedom and less stress about to the patients related to testing, monitoring, and administration of medications.

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