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THE JOURNEY TOWARDS AN ARTIFICIAL PANCREAS

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ABSTRACT
The therapeutic and technological advancements in diabetes treatment has improved the overall quality and longevity of diabetic population.Starting with the syringe for injecting insulin, graduating to insulin pens, insulin pumps, and sensor-augmented pumps advancing towards a hybrid closed loop system ,Insulin delivery technology continues to advance rapidly striving to improve the quality of life of patients. Till the date, insulin syringes are the most widely used insulin delivery technique.Despite the fact that insulin pumps can achieve an appreciable glycemic control compared to insulin pen and syringe, cost affordability andtechnical failure remain as the major challenges. This review discusses about various insulin delivery devices such as insulin syringes , pen , insulin pump and hybrid closed loop system and also novel technological advancements in diabetes care.

I. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that affects almost all age groups which is characterized byhyperglycemia due to impaired insulin production and secretion with or without insulin resistance.Diabetesmay be classified according to aetiology and the most common types being type1diabetes (absoluteinsulin deficiency due to autoimmune destruction of beta cells), type 2 diabetes (associated with genetics, co-morbidities,drugs, or lifestyle changes), and gestational diabetes (hyperglycemia during pregnancy).[11]

Insulin therapy was developed in 1920s . Insulin increases peripheral glucose uptake, protein synthesis in skeletal muscle, gluconeogenesis and lipogenesis, improves glycemic control and reduces the risk of long-term complications of diabetes such as retinopathy, neuropathy and nephropathy.[16]Initially, insulin delivery has been accomplished with large glass syringes and reusable needles.[11]For decades , vial and syringe was the only method for insulin delivery.About 150 million people globally requires insulin therapy for their diabetes management.

The insulin peptide hormone is destroyed by gastric acid secretion when taken orally[21] . Due to its ease of administration, subcutaneous administration is the most commonly recommended method of insulin delivery[9] . Insulin includes slow-acting products, recombinant insulins, fast-acting insulins, intermediate-acting insulins, and long-acting insulins[11]. Although the subcutaneous route of administration is preferred over other routes of administration, limitations such as injection site pain, lipodystrophy, and non-compliance still exist . New drug delivery systems are being introduced to improve drug adherence, safety and efficacy. The first dedicated insulin syringes were introduced in the 1920s, followed by advanced insulin pumps (1963), insulin pens (1985), sensor-assisted pump therapy (2006), and tandem pump-controlled IQ technology (2020) technology was developed[11] . Advances in diabetes technologyhave improved patient compliance andtransformed patient care.

INSULIN SYRINGES

Earlier, big and heavy reusable syringes were used for insulin delivery which required sterilisation by boiling before reuse . Becton Dickinson developed the first specialized syringe for insulin injection in 1924 . In 1925 ,Novo Nordisk's first insulin syringe 'Novo Syringe' was introduced.[11]

The first disposable glass syringe, the hypak™ was introduced in 1954by Becton Dickinson.[5]By the mid 1960s, disposable plastic syringes became available on market . The transition from the commonly practiced 40 units / ml and 80 units /ml insulin syringes to 100 units /ml was a remarkable achievement. Due to the incorrect dosages as a result of inherent dead space in glass syringes, U- 100 plastic insulin syringes came into use followed by U-500 in 2016.

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Currently small bore sized and short needles (8mm , 6 mmand 5 mm) replaced the long , large bore sized and reusable needles which were used in earlier years. Even though , insulin syringes started becoming less popular in the current era , they were the only option for insulin delivery for over 50 years.

Difficulty in injecting insulin multiple times a day , pain and needle associated infections , poor dose accuracy , unpleasant psychological impact , difficulty in conveyance have led to a lack of treatment persistence and non adherence with insulin syringes.[11]

INSULIN PEN

The advent of insulin pen dates back in 1985 which was one of the notable achievementsin insulin delivery.An insulin pen consisted of a disposable insulin needle, an incremental " one click per unit " dose knob and an insulin catridge , . Reusable and disposable pens are available.Disposable pens have prefilled catridge and are discarded after use .Reusable pens have a reusable catridge.Novopen launched by Novo Nordisk was the first insulin pen followed by Novolet , the world's first disposable prefilled insulin pen launched in 1989 .[23] Insulin pens improved user acceptance due to ease of administration ,increased dosage consistency and accuracy ,flexibility ,less injection pain ,increased patient satisfaction and compliance , long term cost effectiveness leading to improved treatment outcome and persistence compared to syringes. Considering the needs of diabetic population ,more sophisticated insulin pens have been developed through technological refinements over the fundamental features of the earlier versions**.** Considering the limited tactile sense and dexterity due to neuropathy, reduced vision, and low hand strength ,many pens have been developed to minimize injection force, thumb extension, and pen diameter, while also ensuring doses.[11]

First-generation insulin pens have been commercializedsince 1990s. Durable pens of the NovoPen family, AllStar (Sanofi), and prefilled pens, such asHumalog Pen, Kwikpen (Eli Lilly),FlexPen, FlexTouch (Novo Nordisk), and SoloSTAR (Sanofi) became the most popular amongthe first generation pens. Novo Nordisk has developed families of reusable/durable and prefilled insulin pens to meet different patient needs, up to the latest NovoPen 6 and NovoPen Echo Plus with SMART technology. Novartis developed the NovoPen 3 PenMate to hide the needle from view, for patients with needle phobia.

Fig 1 : Insulin pen

The advantages of insulin pen was further enhanced by introduction of smart pens with greater adherence , memory support and lower cost.

From insulin pens delivering 100 u/ml , higher concentrated insulin pens were developed for 200U/ml (Humalog, Tresiba) and 300 U/ml (Toujeo/Glargine) which have been in use since 2017.

Second-generation pen devices or ''smart pens'' with a memory features have been developed since 2007. Smart pen's memory features reduced the cognitive load of diabetics by tracking the date , time and amount of previous insulin doses .Eli Lilly's Humapen MEMOIR launched in 2007 was the world's first digital insulin pen with memory which recorded the last 16 insulin doses. This was a major innovation. These devices are digitally connected pens that can store and transmit data to a smartphone via USB or Blue tooth technology regarding insulin dosing.They can also send insulin user reminders and help calculate bolus doses.The first smart pen in the world was the Inpen approved by FDA in 2017 followed by its newer version which provides data about missed doses , the amount of insulin left in the pen , temperature variations that can affect the potency of the insulin.[11]

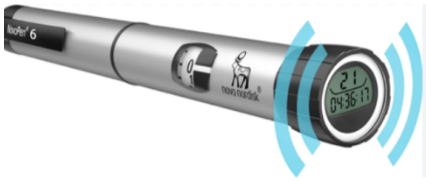

Fig 2 : Smart insulin pen

Another major innovation was insulin pen caps. The insulin pen cap is a lid attatched to an insulin pen that can transmit insulin dosing information to the patient's mobile app.This can also help integrate CGM data and help calculate correction boluses. In 2021 the FDA approved the

Bigfoot Unity Diabetes Management System insulin pen cap for use with the Libre 2 CGM (for patients>12 years of age).Other smart insulin pen caps include GoCap , Insulclock , Timeinsulin etc

Difficulty in applying a mixture of insulins, higher cost, and lack of universal insurance coverage, have been major concerns in the use of insulin pens.Although easy to use, pens have more complex mechanics than insulin syringes. Despite the long-term cost-effectiveness treatment ,with pen is more expensive than insulin syringes.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) OR INSULIN PUMP

Continuous subcutaneous insulin infusion or insulin pump is one of the most notable advancements in diabetic management . It mimics the normal physiologic secretion of insulin by pancreas offering an appreciable glycemic control with better user satisfaction.

The first insulin pump was discovered by Dr. Arnold Kadish in 1963 which resembled a backpack followed by the first portable autosyringe Big Blue Brick developed by Kamon.[11]

There are two types of insulin pumps,Tubed or tethered pumps and patch pumps.Tubed pump has a fine tube that connects insulin reservoir to infusion cannula which is inserted into subcutaneous tissue of upper arms,abdomen,lower back or upper thighs whereas patch pumps are tubeless and directly adheres to the skin and is wirelessly controlled.Insulet introduced the first patch pump in 2011.The insulin reservoir typically stores rapid acting insulin for 2-3 day supply based on patients' insulin requirement.The infusion site has to be changed once every 2-3 days.[3,6]

INDICATIONS OF INSULIN PUMP

Insulin pumps are primarily indicated in patients with Type 1 Diabetes Mellitus with high HbA1C,recurrent hypoglycemia, larger daily insulin requirement, inability to self administer, Presence of complications like gastroparesis and the need for a more mealtime flexibility. It is also used by Type 2 diabetics who cannot achieveglycemic control despite multiple daily injections and lifestyle modifications.About 1/1000 patients are currently using insulin pumps ; 90% have type 1 DM and 10% have type II. [19,17]

Type of insulin used: Usually rapid acting insulin like Lispro,Aspart or Glulisine is used in an insulin pump. Due to risk of catheter occlusions and Diabetic ketoacidosis , Regular insulin is not currently approved for use in insulin pumps.[19]

Delivery of insulin:Insulin can be delivered as basal doses (small doses , continuous) and as mealtime bolus. Basal doses can be preset or auto adjusted hourly based on blood glucose data. depending on physiology,developmental life stage,activity level ,time of day and sleep schedule.Mealtime bolus is determined by the number of carbs as entered into the pump by the patient or clinician. Acorrection bolus can also be preset based on insulin sensitivity factor (ISF).Four main types of boluses include a) typical bolus where insulin is delivered immediately in three minutes on top of basal rate, b) Dual wave bolus in which 30-70% of insulin bolus is delivered as typical bolus and the rest is delivered over a preset time period (2-4 H) c) Square bolus which delivers insulin over an extended predetermined time period (2-4) d) Super bolus in which basal insulin for the next 1-4 H is added to the bolus dose and temporarily suspending insulin delivery during those hours.The square wave bolus is useful indelayed digestion as in gastroparesis, Dual wave bolus is helpful with high protein or fatty diet and superbolus in diet rich in carbohydrates.Pumps allow a precise insulin dosing with bolus doses in increments as small as 0.025 units.40-50% of pump's total daily insulin dose is delivered as basal insulin and the rest is delivered as mealtime bolus.[19]

SENSOR AUGMENTED THERAPY AND AUTOMATED INSULIN DELIVERY

Sensor augmented pump therapy integrates insulin pump and continuous glucose monitoring (CGM)sensors into a single system. A CGM is a device implanted subcutaneously or worn on skin that measures glucose levels in the interstitial fluid every 1-5 minutes depending on the sensor . They can be masked (personal) where glucose data can only be accessed by the patient in real time or professional where glucose data can be downloaded and retrospectively reviewed by a clinician or researcher . The CGM readings are used to adjust insulin delivery through insulin pump.SAP systems were further integrated with hypoglycemic suspension technology such as Threshold suspend(TS) or Low glucose suspend (LGS) and Predictive Low Glucose Suspend (PLGS) which was a stepping stone to the advent of Artificial pancreas.TS suspends the delivery of insulin if the blood glucose levels drop below a preset threshold where as PLGS halts insulin delivery about 30 minutes before hypoglycemia is expected to occur[16].Once the glycemic levels return to normal ,the pump can automatically restart the insulin delivery. In a clinical trial,TS reduced the severity of nocturnal hypoglycemia by 30-40 %and duration of severe hypoglycemia.[23]

HYBRID CLOSED LOOP SYSTEM (ARTIFICIAL PANCREAS)

Automated insulin delivery , also known as hybrid closed loop system (HCL) or artificial pancreas consists of a sensor like CGM that measures blood glucose and sends data to a computer algorithm, (2) a control algorithm to analyze the data and calculate the required basal insulin dose, and (3) an insulin infusion pump to deliver insulin as per the computer instructions.HCL requires the patient to bolus insulin based on carbohydrate intake. Advanced AIDs have the capacity to automate correction doses . Full AIDs can adjust all insulin delivery including prandial . But unfortunately currently no fully automated closed loop systems are available. Insulin On Board (IOB)is another feature in some pumps that can calculate the active insulin remaining in patients' body from previous insulin bolus doses.TheMinimed 670G with a Guardian 3 CGM sensor is the first hybrid closed loop artificial pancreas licensed by FDA in 2017 for T1D therapy in children 7 yrs or older. It uses Proportional Integral Derivative algorithm (PID) to calculate personalised basal insulin. This algorithm alters the rate of insulin delivery based on deviation from target glucose and rate of change of measured glucose. Several other control algorithms such as model predictive control (MPC) algorithms, proportional integral derivative (PID) controllers and fuzzy logic control approaches have been developed.Omnipod 5 approved in 2022 is currently the only tubeless one approved by FDA.[19,22]

Future AIDs may use artificial intelligence to improve individualised diabetes management and performance of the system.

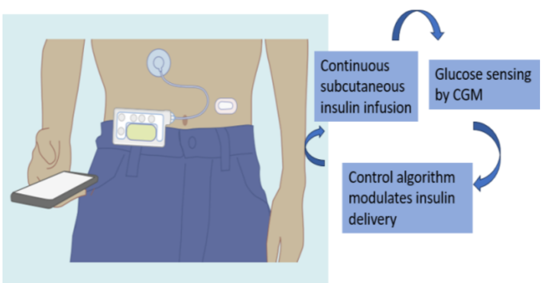

Fig 3: Mechanism of hybrid closedloop system

BENEFITS OF INSULIN PUMPS

Two systematic reviews and Meta analysis studies from 2017 and 2020 found that AID system to be the most effective strategy for achieving target blood glucose concentration.[1]

- Greater reduction in HbA1C levels and fewer hypoglycemic events
- More accurate insulin dosing
- Avoid the need of multiple injections
- Improved quality of life of patients
- It can store abundant data which can be utilised for insulin dose adjustments

Studies show that the use of insulin pumps resulted in achieving an appreciable glycemic control (~0.5 % HbA1C reduction), reduced insulin dosing (~14%) with reduced glycemic variability and fewer occurences of hypoglycemia thus offering an improved patient satisfaction and quality of life.The pump offers more accurate and incredible flexibility in dosing and also avoids the need of multiple daily injections. Basal insulin can be programmed according to the person's activity, the changing daily requirement, hormonal changes, pubertal spurts, stress, illness, travelling, and any other situations thus simulating a human pancreas.[3,10]

LIMITATIONS OF INSULIN PUMPS

- Time lag in sensor glucose values measured in ISF vs Blood
- Delayed absorption of insulin from subcutaneous depot
- Suboptimal analytical accuracy of CGMs in low glucose range
- Higher acquisition cost
- Technical problems such as pump failure ,infusion set failure
- Missing sensor glucose data due to transmission failure
- Glucose sensor overreading and inadvertent insulin delivery
- Leakage of cannulas
- Skin irritation and infection at insertion site
- It can affect patients' self confidence and body image.
- High risk of developing diabetic ketoacidosis resulting from pump failure or interrupted insulin flow due to a damaged infusion set, air in the tubing or infection at the infusion site.
- Hypoglycemic events due to systemmalfunctioning or user error
- Cybersecurity /data protection and privacy
- Patient needs to bolus prandial insulin and adjust correction boluses

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- Carbohydrate loading before exercise can be problematic
- Adequate training and education is needed for the patients as insulin pumps are more complex to setup when compared to a pen or syringe.[11, 10]

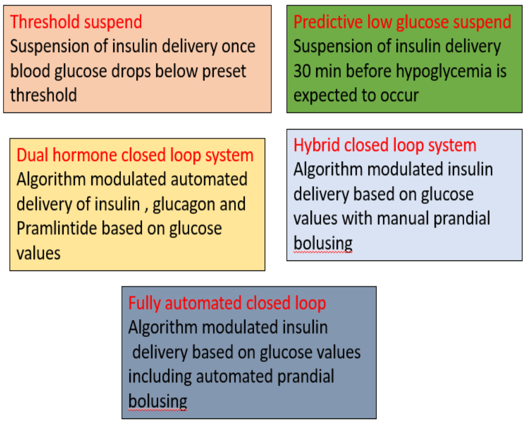

Fig 4: Automated insulin delivery systems

DO IT YOURSELF – ARTIFICIALPANCREAS

Frustrated by the slow and complex regulatory procedures mandatory for the commercialization of closed loop systems , the tech savy diabetes ethusiasts started self building their closed loop systems named ‘ Do it yourself Artificial Pancreas’. It utilises open source algorithms integrated with commercially available CGMs and insulin pumps,currently not approved by FDA.Different diabetes related projects were shared on digital and social media platformswhich has led to their convergence.Three types of DIY -APS are : OpenAPS, AndroidAPS, and Loop. In 2014, Dana Lewis, Scott Leibrand, and Ben West launched the OpenAPS project, the first DIY-APS and in 2017 Pete Schwamb designed ‘‘RileyLink,’’ for his daughter Riley, who had T1D.[11, 10]

BIONIC PANCREAS /DUAL HORMONE CLOSEDLOOP SYSTEM

This closed loop system consists of two infusion pumps separately for glucagon and insulinwhich are delivered based on CGMdata. This can further reduce the risk of hypoglycemia . However complexity of the system, lack of stability of glucagon at room temperature for chronic subcutaneous deliveryand need of two separate infusion systems are the potential limitations.

Dr. Edward Damiano in 2015 invented the first bionic pancreas ‘iLet’ (Beta Bionics), exclusively for T1D treatment which was granted “ breakthrough device recognition” by FDA in 2019. Dual hormone AID systems with insulin and Pramlintide which slow gastric emptying to prevent postprandial hyperglycemia are also being studied. Currently nodual hormone closed loop systems are available although severalare in development.[11]

CONTINUOUS INTRAPERITONEAL INSULIN INFUSION (CIPII)

Since the 1970s, research on the intraperitoneal route of insulin delivery has been conducted.The two distinct technologies in CIPII were implanted intraperitoneal pumps like the MiniMed MIP2 007C (Medtronic) and a percutaneous port connected to an external pump like the AccuChekDiaport system (Roche Diabetes Care). Insulin can be infused into the peritoneal cavity via continuous intraperitoneal insulin infusion (CIPII)The MIP 2007C is put beneath the lower abdominal subcutaneous tissue. The peritoneum is then opened, the catheter tip iscarefully inserted and it is directed into the liver.At least once every three months after implantation, concentrated insulin is transcutaneously applied to refill the pump reservoir at the outpatient clinic.Through the use of an infusion set and an Accu-Chek insulin pump, the AccuChek Diaport system facilitates the infusion of insulin into the peritoneal cavity.For T1D patients who had skin issues andwere unable to effectively control their diabeteswith subcutaneous insulin, this was a good choice .This insulin injection route has certain drawbacks,such as peritoneal infection, cannula blockage, increased cost, and portal-vein thrombosis.In 2007, Medtronic declared the withdrawal ofimplanted insulin pump globally. The Diaport technology can be incorporated into closed-loop insulin administration systems and has comparatively low adverse effects.

NOVEL INSULIN TECHNOLOGIES

- IMPLANTABLE PANCREAS

It is a gel based system that alters the rate of insulin delivery based on blood glucose variation which is under development at De Montfort University. This can improve glycemic outcome with less hypoglycemia and also enhance user acceptance as there would be few technical issues and requires less human interference.[22]

- JET INJECTORS

The advent of jet injectors dates back to 1860s . This syringe delivers insulin subcutaneously with the aid of high air pressure mechanism . Several safety and feasibility studies have been undergoing to evaluate the treatment efficacy and pharmacokinetics and pharmacodynamics of insulin delivered through jet injectors.[11]

- INSULIN INHALERS

The pulmonary route of insulin administration was the first substitute for subcutaneous insulin delivery where in fine insulin is inhaled into lungs. This was a significant innovation to address needle phobia and incorrect injection technique and associated hypoglycemia. The first inhalableinsulin , Exubera (Pfizer) ,introduced in 2006 was withdrawn from market in 2007 due to high cost and dose inaccuracy. Afrezza , a rapid acting insulin powder approved in 2014 is currently the only available inhalable insulin. The acceptance of inhalable insulin is further limited by safety concerns and other competing products.[11]

- Glucose Responsive Insulin systems based on polymers

Inpolymer based systems , native or derivatized insulin has been sequestrised inside a matrix suitable for subcutaneous injection and intregrating glucose responsive components into delivery methods. The matrix detects the amount of glucose present and releases an appropriate quantity of insulin. Three classes of glucose-sensitive motifs have been used: (1) glucose-binding proteins, which include lectins such as concanavalin A (ConA); (2) glucose oxidase, an enzyme that catalyzes the oxidation of glucose to gluconic acid upon proton release, thereby lowering pH and (3) boronate-based chemistries, such as phenylboronic acid (PBA) which form reversible ester linkages with glucose . Apart from these, a recent novel technological advancement anticipates the possibility of endogenous biological systems, such as mannose receptor and even components of the erythrocyte as a 'smart' matrix-based insulin delivery system.[25]

II. CONCLUSION

Starting with the syringe for injecting insulin, graduating to insulin pens, insulin pumps, and sensor-augmented pumps advancing towards a hybrid closed loop system ,Insulin delivery technology continues to advance rapidly striving to improve the quality of life of patients. Till the date, insulin syringes are the most widely used insulin delivery technique.Despite the fact that insulin pumps can achieve an appreciable glycemic control compared to insulin pen and syringe, cost affordability andtechnical failure remain as the major challenges.Future developments should be directed towards more precise dosing mechanisms ,easier integration with digital platforms and affordability . Still we have a long way to go to achieve the ultimate goal of 100 % time -in -range (TIR)and 0 % time below range and a technology affordable to everyone. This mission requires enormous efforts and commitment which would tremendously transform diabetes therapy.

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