Review Article

Recent advances in insulin delivery devices and modes of insulin therapy

Abstract-

The discovery of insulin will be 100 years old in 2021. Insulin, the first diabetic medication, is now the safest and most effective glucose-lowering medication available. Despite its effectiveness, the most important challenge with insulin has been the occurrence of ~~hypoglycemia ,~~hypoglycemia, which has led to the recommendation of optimal dosages in the majority of patients. Insulin delivery device(s) include syringes, pens, and pumps. ~~In the near future~~Soon, artificial pancreas (AP) by the use of a very closed-loop delivery method will be a big step towards advancement of insulin delivery ~~devices .~~devices. This article looks at the invention of syringes, disposable, long-lasting pens, and connected pens. Continuous intraperitoneal insulin infusion (~~CIPII) and~~CIPII) and patch insulin pumps, artificial ~~pancreas~~pancreas, and other medical devices. Hence, insulin administration that is both minimally invasive and non-invasive, as well as physiological, is required. We review the available information on the evolution of insulin delivery systems, focusing on the advantages and disadvantages of technology as well as anticipated advances. Due to the ~~huge~~ wide variety of technological solutions accessible via the international platform, only the most common methods essential to ~~the care of patients are detailed in~~patient care are detailed here in the article.

Keywords- Insulin delivery devices, Diabetes mellitus, insulin pens, insulin pumps, artificial pancreas, inhaled insulin, glycaemic control,

Introduction- Diabetes mellitus is a group of disorders that impact your body's ability to use blood sugar (glucose). Because glucose is a significant source of energy for the cells that make up your muscles and tissues, it is essential to your health. It's also the primary source of

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energy for your brain. Diabetes is becoming more common ~~over~~ in the world. According to the data provided by the International Diabetes Federation, the number ~~pf~~ of diabetic cases in 2011 were 366 ~~million ,~~million, with 552 million predicted by 2030. [1] Despite the fact that Type 2 diabetes mellitus includes 85-95 percent ~~all~~ of all cases of diabetes, the overall number of Type 1 diabetes mellitus patients of various regions of Europe and the United States has climbed by 2-3 percent. [1,2] As a result, diabetes has become one of the world's most common NCD. In 1997, the American Diabetes Association (ADA) suggested the standard category of diabetes as type 1, type 2, other forms, and gestational diabetes mellitus (GDM), ~~which is now~~ the most generally ~~recognised~~recognized and used classification. (1) In most parts of the world, diabetes is becoming a severe public health issue. (3). Insulin is essential for blood glucose control in all patients with type 1 diabetes and a large percentage of those with type 2. Technological innovation and biotechnology have altered the diabetes treatment environment during the last 20 years. There are multiple types of insulin available, ~~as well as~~and several injection schedules. Despite the availability of insulin vials and pens, patient acceptance and glucose readings obtained with single or multiple-dose injection regimens are not to the required ~~level .Many~~level. Many people with severe Type 2 diabetes and all individuals with Type 1 diabetes ~~are in demand of~~demand insulin to keep blood glucose levels within the therapeutic range. Insulin injections under the skin are the ~~commonest~~ most typical mode of administration. It can be delivered subcutaneously using ~~a number of~~several methods, ~~which incorporates~~including vials and syringes, pens, ~~and pumps~~and pumps.

There are various treatment options available for diabetes mellitus~~, ;~~; with the advancement in technology, there have been various emerging modalities for ~~the treatment of~~treating the ~~disease .Let~~disease. Let us look at the various modalities one by one

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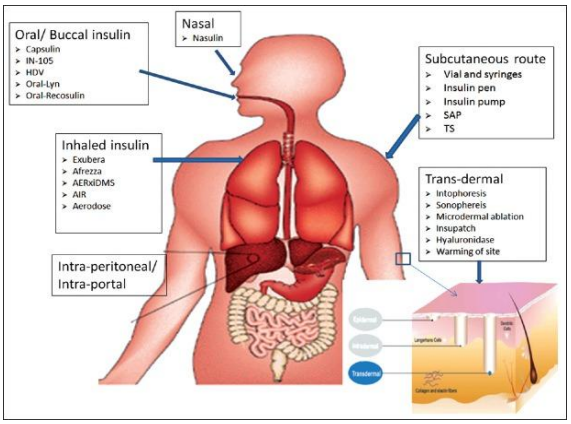

Fig 1. Various modalities

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1.Subcutaneous route- Insulin can be administered subcutaneously in several ways, including vial & syringe, pens, and continuous subcutaneous insulin infusion (CSII).

Vials & syringe –

One of the earliest parenteral ~~strategy~~strategies for drug distribution, which employed syringes and needles, was documented in the later ~~part of~~ 1800s, whereas the injections under the skin route ~~was~~ were discovered in the early 2000s. Becton, Dickinson and Company (BD) developed an insulin injection syringe two years later to ~~the its~~its ~~discovery ,~~discovery. [4] Syringes were once made of metals and/or glass, were reusable, and had to be ~~sterilised~~sterilized after each use by boiling. To reduce the number of infections caused by needles, disposable syringes were ~~developed.The~~developed. The injection port i-port Advance® was recently developed. It~~'~~'s the first device to integrate ~~a~~ an I port for ~~njection~~injection -and an inserter into one device, reducing the number of syringes needed and removing the necessity for skin pricks for each dosage. This gadget is ~~useful~~ helpful for insulin-dependent people who are afraid of needles ~~but yet~~but want ~~a controlled blood~~controlled blood ~~sugar (~~sugar. (5)

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Limitations-

Despite ~~all of~~all the foregoing advancements, most patients had trouble injecting insulin numerous times per day [6]. Furthermore, the use of syringes has been

linked to poor dosage accuracy, a lengthy training time, an unpleasant psychologic impact, and conveyance issues [7]

Insulin pens-

Pens, in comparison to syringes, provide simpler, precise, and convenient insulin administration. An insulin pen ~~is made up of~~comprises three parts: a cartridge for insulin, a ~~needle which is disposable ,~~disposable needle, and a single-click per unit dosage system. ~~It is possible for the gadget to~~to. The gadget can be reusable or disposable. It gives patients greater freedom, discretion, and long-term cost-effectiveness, all of which help the patients stick to your treatment plan. As a result, insulin pens provide better blood glucose regulation and are becoming more generally adopted. (8) Novo Nordisk introduced the NovoPen, the first insulin pen, in 1985. Pens of the first generation have been on the market since the 1990s. Many generations of durable NovoPen pens, AllStar (Sanofi), and prefilled pens like FlexPen and Kwikpen are among the popular insulin pens of this type. The NovoPen 3 is a long-lasting pen with ~~a~~an optimum dose of 70 Units. It was brought to the market in 1992. In 2012, Sanofi India debuted AllStar, the country's first indigenously made reusable insulin pen, ~~which is~~ particularly tailored for diabetic patients.

Next-Generation Insulin Pens-Since 2007, next-generation pens with memory features, sometimes known as "smart pens," have been on the market. These devices contain a multidose memory feature that saves the date, time, and dosage of prior administrations. [9]. For optimal monitoring and data management, these gadgets include USB or Bluetooth connectivity.

Connected pens- these pens are the next advancement in the category of ~~pens ,which~~pens, which includes ~~peoperties~~properties that go far beyond memory. The InPen System, a Bluetooth-enabled wireless pen with a device interface and advisor about bolus, was introduced by Companion Medical in 2017 [10]. This collection of pens includes Novo Nordisk's "soon to be launched" NovoPen 6 and NovoPen Echo Plus.

Disadvantages- The limitations, like ~~The~~the difficulty of combining insulins, the ~~greater cost~~higher cost, have all been major sources of concern. [11]. Insulin pens are more difficult to use mechanically than insulin syringes, despite their apparent

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simplicity. [12] Pen device therapy is more expensive than vial therapy when long-term economical effectiveness is ignored, as observed in in low- and middle-income nations[nations [13]. Table A highlights some main benefits and drawbacks of pen.

Table A : Disadvantages and Advantages of pens and pumps

Device	Advantages	Disadvantages
Insulin pen	Discreet Insulin administration that is both efficient and simple Accurate dosing Injection Ease Time saving It is feasible to be versatile due to the disposable and reusable options. Simple to transport Improved treatment adherence Cost-effectiveness over time	In low-income nations, syringes are more costly. For the first time, syringes are more costly. It is not possible to blend various insulin kinds. Dosage is kept low.
Insulin pump	Utilization of a regular insulin regimen Ensures sustained insulin delivery Close similarity to physiologic insulin delivery Allows for greater lifestyle freedom	Cannula and infusion set technical and safety concerns (detachment, crimping, or leaking) Patients may have skin irritation or hypersensitivity as a result ofbecause of cannula and infusion set technical and safety difficulties (detachment, crimping,leakagecrimping, leakage). More patient engagement and compliance are required. More patient engagement and compliance are required.

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		More expensive

Insulin Pumps (Continuous Subcutaneous Insulin Infusion-CSII)

One of the most efficient ways to supply exact doses of rapid-acting insulin to meet the body's ~~body's~~ demands ~~is~~ to use an insulin pump, also known as CSII. [14] An insulin pump is made up of-

3 parts: 1. an insulin reservoir, 2. an infusion set, and 3. tube

The insulin reservoir is linked to an infusion set and a catheter, which constantly injects dosage depending on user-specific programming to meet daily demands. Before meals, the pump can provide insulin in both basal (slow, continuous) and incremental (bolus) dosages. [17]

Multiple Daily Injections (MDI) have been extensively ~~used in~~used in the care of diabetes ~~patients since~~patients since the 1970s~~,~~, when it was initially introduced as a strategy for establishing and maintaining stringent blood glucose control in people with T1DM. [14,15].The insulin pump and the MDI have been ~~utilised~~utilized to treat diabetes ~~in both~~ the juvenile and adult populations. [15.16] Several studies have shown that CSII therapy improves glycaemic control over MDI treatment.~~–~~ Glycaemic management is critical for preventing long-term diabetic consequences. The usage of insulin pumps in ~~paediatric~~pediatric T1DM patients has expanded dramatically, from 1.3 percent in 1995 to 47 percent in 2016. [18] Pumps are routinely utilized to replace insulin in young T1DM patients [19], but they are also commonly ~~utilised~~utilized in T2DM patients. In ~~diabetics~~people with diabetes, CSII treatment improves glycemic and metabolic control (lowering HbA1c, glycemic fluctuation, and low blood sugar). [20]

The most current ~~generation of~~ external pumps, which debuted in the 1990s, are tiny, compact, convenient, and efficient. Bolus calculators, computer connectivity, and warnings are all included in these "smart pumps." [21] Medtronic created the first "intelligent" pump in 2003. This system includes a MiniMed Paradigm 512 insulin pump and a BD-developed

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Paradigm Link glucose monitor. The glucose readings from the glucometer are sent to the pump remotely and automatically in this situation, and the appropriate insulin doses are computed using a Bolus Wizard calculator. [22].

Patch pumps- Because of the limitations of infusion sets~~,~~ "patch pumps" have been developed: pumps that do not require infusion sets, are compact and lightweight with an adhesive that adheres to the skin. Patients benefit from patch pumps because they give more comfort and flexibility, which is critical while travelling. Insulet released the OmniPod, in 2011, the first insulin pump without ~~the need of~~ a tube. It includes an infusion set ~~as well as~~and an automated inserter that communicates wirelessly with a blood pressure monitor.

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Continuous intraperitoneal insulin infusion (CIPII)- Since the 1970s, researchers have been looking into the intraperitoneal modes of insulin delivery. Continuous intraperitoneal insulin infusion (CIPII) allows insulin to be infused into the peritoneal cavity. This technique has the benefit of closely resembling physiology more than other conventional treatments.[23]

Sensor-augmented pump devices-

Since advancements in continuously ~~delivering glucose~~delivering glucose monitors (CGM), it is ~~now~~ possible to make both devices one for diabetes-management systems (pump and CGM). CGMs have ~~shown improvement in~~improved T1DM patients' blood sugar control, and newer devices are more accurate and smaller. [24,25] Sensor-augmented pump (SAP) therapy is when CGM data is used to alter insulin dosage using an insulin pump. In T1DM individuals, SAP decreases A1c by 0.7-0.8 percent ~~when~~ compared to baseline or MDI treatment. [26,27] In order to modify insulin pump administration based on CGM glucose measurements, SAP requires compliance by the patient. ~~In order to~~To modify insulin pump administration based on CGM glucose measurements, SAP requires patient participation. Therefore, SAP is susceptible to human error. Further, SAP medication requires patients' awakening ~~in order to~~to manage low blood sugar during the night.

Sensor-augmented pumps with hypoglycaemic suspend~~s~~ or threshold suspend pumps-

In individuals with T1DM, low blood sugar is the most dreaded immediate consequence of treatment with insulin. ~~Majority of~~Most times hypoglycemia occurs at night, and nocturnal

hypoglycemia is responsible for 6% of mortality in younger people with T1DM. [28,29] Furthermore, the MDI, CSII, and SAP are incapable of eradicating nocturnal hypoglycemia. To decrease nocturnal hypoglycemia, the initial stage in developing an artificial pancreas is to stop treatment once CGM glucose falls below ~~the~~ a certain level (usually 70 or 60 mg/dl). If the user fails to respond to a low glucose warning, the device will stop administering insulin for up to two hours. This function's purpose is to reduce the severity and duration of hypoglycemia, not to avoid it. [30] Insulin suspension for two hours does not cause severe hyperglycemia or diabetic ketoacidosis, nor does it increase the risk of ketone generation. [31] The clinical studies showed that, threshold suspended pumps lowered the hypoglycemia severity at night by 30-40% and the time duration of severe hypoglycemia by 30-40% without affecting HbA1c levels. [32,33]

Limitations-The main disadvantages of infusion sets are that they frequently detach, leak, or cause skin irritation, making insulin pumps more difficult to use [36]. The downsides of CSII treatment include~~s~~ a greater price than MDI, a larger risk of subcutaneous infections, the inconvenient nature of being attached to a device, and a theoretically higher risk of diabetic ketoacidosis. [34] To avoid these problems, patient education before ~~to~~ commencing CSII treatment is ~~critical.[~~critical. [37] Patients ~~had itching and aseptic condition~~ regulary had itching and aseptic conditions at the site of insertion ~~on a regular basis~~. Implanted cannulas kinking, bending, or crimping, as well as infusion set leakage, have all been documented. [36]. ~~When~~ compared to MDI, pump treatment has higher initial and total yearly expenses.

2.Artificial pancreas-

CSII's main goal since its inception has majorly been to create an artificial ~~pancrea~~pancreas that can mimic optimal sugar management with minimum human participation. A "closed-loop" artificial pancreas combines cutting-edge technology with automation to achieve glycemic goals. In general,

The AP connects three devices: (1) a sensor, such as a continuous glucose monitor (CGM), that monitors blood sugar levels and sends data to ~~a~~ software, (2) a computer program~~me~~ that analyses data and determines the appropriate insulin dosage~~–~~, and (3) an insulin infusion pump that delivers insulin as directed by the computer. [34] In 2017, the FDA

~~authorised~~authorized the MiniMed 670G insulin pump with Guardian 3 sensor as the first hybrid closed-loop device for T1D therapy in children aged 7 and higher.

The following will be the next phases in the advancement of the artificial ~~pancreas[~~pancreas [35]:

(1) Using ~~predictive plans~~predictive plans to reduce hypoglycaemia before it arises.

(2) The use ~~of planned~~of planned methods to keep blood sugar levels within the intended range (hypoglycaemia or hyperglycaemia minimizer).

(3) Automated basal ~~closed loop~~closed loop

(4) Fully automated single or multiple (insulin) or multiple (insulin) or multiple

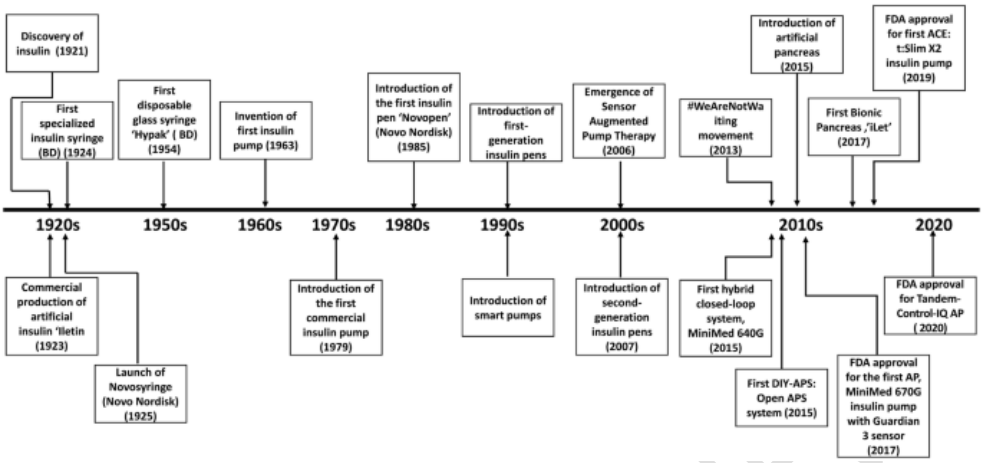
(5) Dual hormonal ~~close loop~~close loop (insulin + glucagon).

3. ORAL ROUTE-

Oral insulin administration is more patient-friendly and more nearly resembles physiological insulin ~~delivery .~~delivery.[38] Proteolytic enzymes in the gastrointestinal system inactivate~~s~~ it, ~~as well as~~and lower permeability across Insulin's larger size and hydrophobicity cause damage to the intestinal membrane, produce low bioavailability. Several pharmaceutical firms are working on carriers that shield insulin from GI breakdown and improve intestinal insulin transport, allowing for appropriate bioavailability when ~~it is~~ delivered to the circulation. (39)

As insulin carriers or vehicles, natural and manufactured nanoparticles such as chitosan, liposomes, polymeric nanovesicles, polylactides, polyalkyl cyanoacrylate, and other polymeric hydrogels have been employed. (40)

Fig 2. The key turning points in the history of insulin delivery methods are graphically represented here.



4.~~Insilin~~ Insulin inhaling devices-

~~The respiratory mode of insulin administration , because~~ Because it was closer to physiologic portal delivery, ~~it~~ the respiratory mode of insulin administration was the first alternative to the subcutaneous method of insulin administration. ~~.Insulin~~. Insulin inhaling devices help patients breathe perfectly ~~alright~~ all right pulmonary ~~insulin~~(insulin (solution-based formulations or powder-based formulations) in the respiratory tract. [41] Inhalable insulin was first offered to the market in 2006 as a critical advancement to combat needle phobia and poor insulin injection processes in systemic insulin delivery systems. Inhalable insulin has ~~useful~~ a proper treatment of postprandial hyperglycemia. [42]. In 2006, the Food and Drug Administration approved Exubera (Pfizer) as the first inhalable insulin ~~for the treatment of~~to treat T1D and T2D. ~~Exubera use, on~~On the other hand, Exubera use has been linked to an increased risk of low blood sugar. Due to its ~~excessive~~ high cost and dosage error, the drug was removed ~~off the market~~ in 2007. Afrezza, a fast-acting Technosphere insulin powder, is the lone survivor in this group (MannKind Corp.). Afrezza was ~~authorised~~authorized by the FDA in 2014 for the treatment of prandial insulin. [43]. Afrezza's administration method is compact and convenient, and it displays the dose in units [44]. In T1D patients, Afrezza has been proven to enhance glycemic control and ~~minimise~~minimize hypoglycemia. [45]. Insurance restrictions, safety concerns, and rival products further limit the acceptance of inhalable insulins [44].

5.Transdermal-

The hazards connected with injections are eliminated with transdermal insulin delivery~~., and the~~. The skin's enormous surface area makes it an ideal route for insulin delivery. [46] Insulin ~~is unable to~~cannot enter the stratum corneum, the outermost layer of the skin. To get through the stratum corneum barrier, several ways have been investigated. [46] Skin damage, burn or blister development, and seldom substantial pain and suffering restrict transdermal insulin administration systems. The technologies are still in development, and the long-term use, safety, as well as usefulness remain unknown.

There are numerous methods for delivering insulin transdermally, including: (a)iontophoresis, a technique that employs tiny electric currents, [47]

(b)Ultrasound waves are used in ~~sonophereis~~sonophoresis or ~~phonophereisis~~phonophoresis.[48]

(c) Microdermal ablation is possible once the stratum corneum is removed. [49]

(d) Electroporation is a procedure that involves delivering a high-voltage pulse for a brief length of time. [50]

(e) Insulin is contained in a transferosome, ~~which is~~ an elastic, flexible vesicle that squeezes itself into skin pores to carry drugs. [51]

(f) InsupatchTM is an insulin pump add-on device that uses ~~localised~~localized heat to boost insulin absorption. [52]

Conclusion- Despite the fact that subcutaneous insulin administration is the most common, it has been linked to injection discomfort, needle phobia, lipodystrophy, noncompliance, and peripheral hyperinsulinemia. As a result, minimally invasive or non-invasive insulin delivery that is also physiological is required. Though there were some laudable advancements in the already available technologies, many of them were unreasonably costly. Each route and delivery technique has its own set of possible benefits and drawbacks. Alternative methods of delivery, if effective, might change the treatment of diabetes mellitus and assist enhance patients' quality of life. This brief essay depicts a shifting dynamic in the insulin delivery devices market's incorporation of digital health technologies.

COMPETING INTERESTS DISCLAIMER:

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Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly ~~use products in our area of research~~used in our research area and country. There is ~~absolutely~~ no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for ~~any~~ litigation but ~~for~~ the advancement of knowledge. Also, the research was not funded by the producing company rather, it was funded by the personal efforts of the authors.

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