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 , 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, artificial pancreas (AP) by the use of a very closed-loop delivery method will be a big step towards advancement of insulin delivery devices . This article looks at the invention of syringes, disposable, long-lasting pens, and connected pens. Continuous intraperitoneal insulin infusion (CIPII) and patch insulin pumps, artificial 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 variety of technological solutions accessible via the international platform, only the most common methods essential to the care of patients are detailed in 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 energy for your brain. Diabetes is becoming more common over the world. According to the

data provided by the International Diabetes Federation, the number pf diabetic cases in 2011 were 366 million , with 552 million predicted by 2030. [1] Despite the fact that Type 2 diabetes mellitus includes 85-95 percent 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 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 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 people with severe Type 2 diabetes and all individuals with Type 1 diabetes are in demand of insulin to keep blood glucose levels within the therapeutic range. Insulin injections under the skin are the commonest mode of administration. It can be delivered subcutaneously using a number of methods, which incorporates vials and syringes, pens, 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 the disease .Let us look at the various modalities one by one

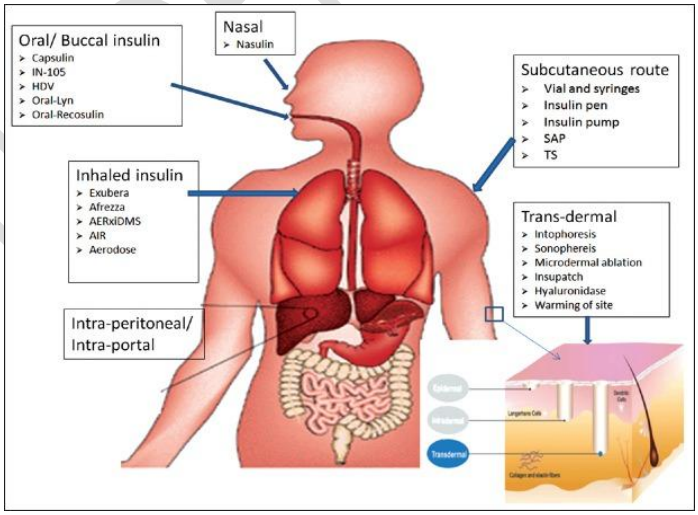


Fig 1. Various modalities

1.<u>Subcutaneous route</u>- 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 for drug distribution, which employed syringes and needles, was documented in the later part of 1800s, whereas the injections under the skin route was discovered in the early 2000s. Becton, Dickinson and Company (BD) developed an insulin injection syringe two years later to the its discovery . [4] Syringes were once made of metals and/or glass, were reusable, and had to be sterilised after each use by boiling. To reduce the number of infections caused by needles, disposable syringes were developed.The injection port i-port Advance® was recently developed. It's the first device to integrate a I port for njection 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 for insulin-dependent people who are afraid of needles but yet want a controlled blood sugar (5)

<u>Limitations-</u>

Despite all of 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 three parts: a cartridge for insulin, a needle which is disposable , and a single-click per unit dosage system. It is possible for the gadget to 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 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 includes peoperties 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 difficulty of combining insulins, the greater cost have all been major sources of concern. [11]. Insulin pens are more difficult to use mechanically than insulin syringes, despite their apparent 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[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	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.

	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	
Insulin pump	Utilization of a regular insulin regimen Ensures sustained insulin delivery Close similarity to physiologic insulin delivery	Cannula and infusion set technical and safety concerns (detachment, crimping, or leaking) Patients may have skin irritation or hypersensitivity as a result of cannula and infusion set technical and safety difficulties (detachment, crimping,leakage). More patient engagement and compliance are required. More patient engagement and compliance are required. More expensive

	Allows for greater lifestyle freedom	

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 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 care of diabetes 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 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 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 in T2DM patients. In diabetics, 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

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 an automated inserter that communicates wirelessly with a blood pressure monitor.

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 monitors (CGM), it is now possible to make both devices one for diabetes-management systems (pump and CGM). CGMs have shown improvement in 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 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 manage low blood sugar during the night.

Sensor-augmented pumps with hypoglycaemic suspends or threshold suspend pumps-

In individuals with T1DM, low blood sugar is the most dreaded immediate consequence of treatment with insulin. Majority of 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 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 includes 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.[37] Patients had itching and aseptic condition 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 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 programme 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 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[35]:

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

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

(3) Automated basal closed-loop

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

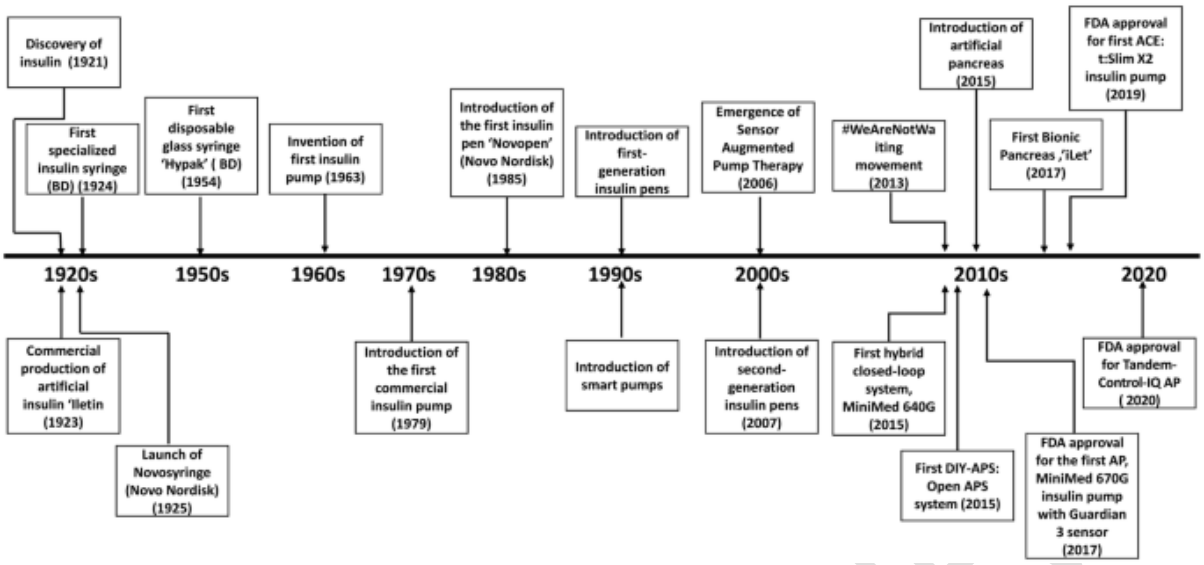
(5) Dual hormonal close-loop (insulin + glucagon).

3. ORAL ROUTE-

Oral insulin administration is more patient-friendly and more nearly resembles physiological insulin delivery .[38] Proteolytic enzymes in the gastrointestinal system inactivates it, as well as 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 inhaling devices-

The respiratory mode of insulin administration , because it was closer to physiologic portal delivery, it was the first alternative to the subcutaneous method of insulin administration .Insulin inhaling devices help patients breathe perfectly alright pulmonary 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 treatment of postprandial hyperglycemia. [42]. In 2006, the Food and Drug Administration approved Exubera (Pfizer) as the first inhalable insulin for the treatment of T1D and T2D. Exubera use, on the other hand, has been linked to an increased risk of low blood sugar. Due to its excessive 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 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 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 skin's enormous surface area makes it an ideal route for insulin delivery. [46] Insulin is

unable to 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 or phonopheresis.[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 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:

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 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 personal efforts of the authors.

References –

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;**37 Suppl 1**:S81–S90.

2 .Garg SK, Michels AW, Shah VN. Use of non-insulin therapies for type 1 diabetes. Diabetes Technol Ther. 2013;15:901–8.

3.Whiting D.R., Guariguata L., Weil C., Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res. Clin. Pract. 1999;94:311–321. doi: 10.1016/j.diabres.2011.10.029.

4 .Milestones BD. [Last accessed on 2013 Sep 16].

5. Burdick P, Cooper S, Horner B, Cobry E, McFann K, Chase HP. Use of a subcutaneous injection port to improve glycemic control in children with type 1 diabetes. Pediatr Diabetes. 2009;10:116–9. [PubMed] [Google Scholar]

6. Shah RB, Patel M, Maahs DM, Shah VN. Insulin delivery methods: past, present and future. Int J Pharm Investig. 2016;6:1–9.Return to ref 16 in article

7. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol. 2010;4:522–531.

8. Guerci B, Chanan N, Kaur S, Jasso-Mosqueda JG, Lew E. Lack of treatment persistence and treatment nonadherence as barriers to glycaemic control in patients with type 2 diabetes. Diabetes Ther. 2019;10:437–49.

9.Healthworld.com. Eli Lilly launches 200 U/mL pre-filled insulin pen. Econ Times.

10. Bailey TS, Stone JY. A novel pen-based Bluetooth-enabled insulin delivery system with insulin dose tracking and advice. Expert Opin Drug Deliv. 2017;14:697–703.

11. MedicalNewsToday. What are insulin pens and how do we use them?

12. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol. 2010;4:522–531.

13. Ewen M, Joosse H-J, Beran D, Laing R. Insulin prices, availability and affordability in 13 low-income and middle-income countries. BMJ Glob Health. 2019;4:e001410.

14. Moser, EG, Morris, AA, Garg, SK. Emerging diabetes therapies and technologies. Diabetes Res Clin Pract. 2012;97:16-26.

15. Bruttomesso, D, Pianta, A, Crazzolara, D, et al. Continuous subcutaneous insulin infusion (CSII) in the Veneto region: efficacy, acceptability and quality of life. Diabet Med. 2002;19:628-634.

16. Jeitler, K, Horvath, K, Berghold, A, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008; 51:941-951.

17. Medtronic. What is insulin pump therapy. Medtronic.

18.Karges, B, Schwandt, A, Heidtmann, B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA. 2017;318:1358-1366.

19. Hieronymus Laura GS. Insulin delivery devices. Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, Hazenfield RM

Diabetes Care. 2011 Mar; 34(3):574-9.

20. Pickup JC, Reznik Y, Sutton AJ. Glycemic control during continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: individual patient data meta-analysis and meta-regression of randomized controlled trials. Diabetes Care. 2017;40:715–22.

21. Skyler JS, Ponder S, Kruger DF, Matheson D, Parkin CG. Is there a place for insulin pump therapy in your practice? Clin Diabetes. 2007;25:50–6.

22. edtronic. Innovation milestones. https://www.medtronicdiabetes.com/about-medtronic-innovation/milestone-timeline (2020).

23. Garcia-Verdugo R, Erbach M, Schnell O. A new optimized percutaneous access system for CIPII. J Diabetes Sci Technol. 2017;11:814–21.

24. Merging diabetes therapies and technologies.Moser EG, Morris AA, Garg SK

Diabetes Res Clin Pract. 2012 Jul; 97(1):16-26.

25. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study.

Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, Hazenfield RM

Diabetes Care. 2011 Mar; 34(3):574-9.

26. Improved glycemic control through continuous glucose sensor-augmented insulin pump therapy: prospective results from a community and academic practice patient registry.

27. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes.

Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA, STAR 3 Study Group.
N Engl J Med. 2010 Jul 22; 363(4):311-20.

28. Dead-in-bed syndrome in young diabetic patients.Sovik O, Thordarson H

Diabetes Care. 1999 Mar; 22 Suppl 2():B40-2.

29. Severe hypoglycemia predicts mortality in diabetes.Cryer PE

Diabetes Care. 2012 Sep; 35(9):1814-6.

30. The ASPIRE study: design and methods of an in-clinic crossover trial on the efficacy of automatic insulin pump suspension in exercise-induced hypoglycemia.Brazg RL, Bailey TS, Garg S, Buckingham BA, Slover RH, Klonoff DC, Nguyen X, Shin J, Welsh JB, Lee SW

J Diabetes Sci Technol. 2011 Nov 1; 5(6):1466-71.

31. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study.

Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR

Diabetes Technol Ther. 2012 Mar; 14(3):205-9.

32. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy.

Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, Bläsig S, Wadien T, Zierow S, Hartmann R, Thomas A

Diabetes Technol Ther. 2011 Nov; 13(11):1129-34.

33. Threshold-based insulin-pump interruption for reduction of hypoglycemia.

Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR, ASPIRE In-Home Study Group.

N Engl J Med. 2013 Jul 18; 369(3):224-32.

34. Story of discovery—artificial pancreas for managing type 1 diabetes: cutting-edge technology 50 years in the making. Natl Inst Diabetes Dig Kidney Dis. 2017. https://www.niddk.nih.gov/news/archive/2017/story-discovery-artificial-pancreas-managing-type1-diabetes.

35. Closed-loop system in the management of diabetes: past, present, and future.

Shah VN, Shoskes A, Tawfik B, Garg SK

Diabetes Technol Ther. 2014 Aug; 16(8):477-90.

36. Heinemann L, Krinelke L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. J Diabetes Sci Technol. 2012;6:954–964. https://www.ncbi.nlm.nih.gov/pubmed/22920824.\

37. Emerging diabetes therapies and technologies.

Moser EG, Morris AA, Garg SK
Diabetes Res Clin Pract. 2012 Jul; 97(1):16-26.

38.Arbit E, Kidron MJ Diabetes Sci Technol. 2009 May 1; 3(3):562-7

39. Oral Delivery of Insulin: Novel Approaches. [Last accessed on 2013 Nov 10]

40. Sonia TA, Sharma CP. An overview of natural polymers for oral insulin delivery. Drug Discover Today. 2012;17:784–92.

41. Shah RB, Patel M, Maahs DM, Shah VN. Insulin delivery methods: past, present and future. Int J Pharm Investig. 2016;6:1–9.

42. Santos Cavaiola T, Edelman S. Inhaled insulin: a breath of fresh air? A review of inhaled insulin. Clin Ther. 2014;36:1275–89.

43. Heinemann L, Baughman R, Boss A, Hompesch M. Pharmacokinetic and pharmacodynamic properties of a novel inhaled insulin. J Diabetes Sci Technol.

44. Oleck J, Kassam S, Goldman JD. Commentary: why was inhaled insulin a failure in the market? Diabetes Spectr. 2016;29:180–184.

45. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther. 2018;20:639–47.

46. Transdermal drug delivery.Prausnitz MR, Langer R

Nat Biotechnol. 2008 Nov; 26(11):1261-8.
47. Iontophoresis-based transdermal delivery systems.Kanikkannan N

BioDrugs. 2002; 16(5):339-47.
48. Iontophoresis-based transdermal delivery systems.Kanikkannan N

BioDrugs. 2002; 16(5):339-47.
49. Transdermal insulin delivery using microdermabrasion.

Andrews S, Lee JW, Choi SO, Prausnitz MR
Pharm Res. 2011 Sep; 28(9):2110-8.

50. Electroporation: an avenue for transdermal drug delivery.

Charoo NA, Rahman Z, Repka MA, Murthy SN

Curr Drug Deliv. 2010 Apr; 7(2):125-36.

51. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery.

Malakar J, Sen SO, Nayak AK, Sen KK

Saudi Pharm J. 2012 Oct; 20(4):355-63.

52. Increasing local blood flow by warming the application site: beneficial effects on postprandial glycemic excursions.

Freckmann G, Pleus S, Haug C, Bitton G, Nagar R

J Diabetes Sci Technol. 2012 Jul 1; 6(4):780-5.