MMJ

Malta Medical Journal, 2025; 37(2)
http://mmsjournals.org/index.php/mmj/44

REVIEW ARTICLE

Insulin - The Modern Era

Maria Mizzi, Simon Mifsud

Insulin – a naturally occurring hormone produced by beta cells in the pancreas, has been successfully isolated and purified in the year 1921 by the scientists Banting and Best in Toronto. Since then, more than 100 years later, different formulations and delivery methods have been developed. Type 1 diabetes depends on insulin for survival and reduced morbidity. Therefore, it came naturally with time to research newer technologies that mimic as much as possible the job of the pancreatic beta cells to provide insulin. This led to the development of the first model of continuous subcutaneous insulin infusion in the 1970s. Several advantages have been linked to the insulin pump as opposed to multiple daily insulin injections. Literature mentions better glycaemic outcomes with increased time in range and reduced hypoglycaemic episodes with insulin pumps. Other benefits vary from practical and psychological benefits with regards to the changing mentality towards living with type 1 diabetes, to long-term benefits involving the reduction of micro- and macrovascular complications. Studies are still being conducted to determine whether type 2 diabetic patients could also benefit from such insulin pumps.

Dr Maria Mizzi, MD, MRCP(UK)
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

Dr Simon Mifsud, MD, MRCP(UK)
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

The years 1921 and 1922 saw one of the biggest discoveries in medical history – the discovery of insulin by Banting and Best in Toronto.[1] Prior to the isolation and administration of exogenous insulin, a diagnosis of type 1 diabetes meant a shorter life span, seeing a lot of childhood deaths within 1-2 years from disease onset. Mortality data from a clinic in Boston, Massachusetts concluded that death in young type 1 diabetic patients in their first decade of life has decreased by six times following the availability of insulin in clinical practice.[2] Following the 23rd January 1922 when insulin was first successfully administered to a 14 year old boy – Leonard Thompson in Toronto General Hospital, clinical improvement was immediate and every child with diabetic ketoacidosis (DKA) started showing immediate improvement with Leonard Thompson himself managing to survive a further 13 years after this day. It was only after May 1922, that by the agreement with the pharmaceutical company Eli Lilly, insulin started to be produced on a larger scale to target more patients.[1]

Despite being a drug that literally saved dying children, insulin in its very first days saw a lot of challenges when it came to administration, dose titration and monitoring of its effect. These challenges nowadays are almost unheard of thanks to the evolution of both the drug itself, with the introduction of recombinant human insulin with various modes of action such as short or long acting; and also other technologies surrounding administration and monitoring.[1] Technology has improved in such a way that insulin administration has moved from syringes, to pens and continuous subcutaneous insulin pumps. The concept of insulin pumps goes back to 1963 when Dr. Arnold Kadish designed the first prototype that was less portable than what we are used to nowadays. It was then only in the 1980s that the subcutaneous insulin pump with adequate programmability and portability became available on the market. And since then, technology kept improving to the point that nowadays, there are insulin pumps available that contain a system of continuous blood glucose monitoring whereby blood glucose readings are channelled to the pump itself which calculates and administers prandial insulin boluses – the so called Advanced Hybrid Closed Loop (AHCL) systems.[3,4]

DISCUSSION

The way a continuous subcutaneous insulin infusion works is by mimicking the pancreas by providing a continuous release of short acting insulin (the basal rate), and then gives the possibility to administer larger boluses close to meals.[3,5] The crucial difference compared to the pancreas comes from the fact that the exogenous insulin administered in the fat tissue gets transported to muscle, bypassing the liver. Endogenous insulin on the other hand finds its way to the liver via the portal circulation. This way, there is homeostatic regulation of insulin levels to be able to exert the full desired action peripherally and eventually insulin clearance.[6]

Basal insulin has the aim to control blood glucose during fasting hence replacing the use of long-acting insulin formulations. The basal insulin rate is influenced by many variables including physiology, developmental life stage, activity level, and time of day.[5] In fact, this is usually set in the pump after discussing with ones Diabetologist. Certain pumps have the facility to programme multiple basal insulin rates which can be chosen then by the patient depending on the specific daily activities.[7] This is especially helpful during periods of acute illness or strenuous exercise. As a rule, 30-50% of the total insulin dose administered in one day should be in the form of basal insulin, with the rest being boluses administered with meals. The prandial boluses can be administered either as an immediate insulin dose over a short time, or over a longer period of time (extended bolus) depending on how the pump is programmed. The extended bolus is particularly beneficial in association with the consumption of high fat and/or protein meals. Such prandial bolus doses can be calculated according to oral intake and using the facility of bolus calculators which are incorporated in most insulin pumps available on the market.[5]

Although there are various insulin pumps on the market, these essentially consist of a reservoir of insulin which is either connected directly to the subcutaneous tissue via a cannula – the so-called "patch pump"; or else, insulin would be delivered via a tubing system to the cannula in the subcutaneous tissue.[8,9] All systems available are battery-operated and there are both non-automated as well as automated systems available.[5,8] The Food and Drug Administration (FDA) of the United States has approved Lispro and Aspart for usage in insulin pumps which can stay in the reservoir for a maximum of 144 hours. Other short-acting formulations of insulin would have different shelf lives depending on the risk of crystallisation, etc. The insulin pump can deliver a basal insulin rate at various rates with the lowest rate being that of 0.01 unit/hour.[9]

The initial cost for an insulin pump varies between around €2300 and €3500, depending on the brand one buys and the features available.[10] Apart from this initial cost for a pump that is set to last at least five years, there is an additional cost of around €1100-€2300 yearly in tubing, cannulas, and other pump exchangeable parts (excluding other equipment such as adhesives, pump pouches, etc.). This yearly cost also excludes the supply of insulin itself, which in countries where treatment is not available on the formulary can amount to thousands per year.[7,10] Considering the price, this could be a limiting factor to the transition from multiple daily insulin injections (MDI) to the insulin pump, especially in cases where patients fail to have medical insurance cover. Also, the need for trained healthcare professionals to safely run such a service limits the setting up with a large number of patients.[5]

Such systems have the advantage that patients tend to accept it better with improved compliance.[3] Also, with regards to food, it allows for better precision of insulin administration as the pump is able to administer smaller doses of 0.05-0.1 units as compared to the 0.5-1 units administered using a syringe or pen. Therefore, improving blood glucose readings as well as eliminating the need for snacking to prevent hypoglycaemic events.[5] Disadvantages associated with this system include local skin reactions and the need for good training and motivation from the patient's side before introducing such system.[3] Also, one needs to take into consideration, the patient's willingness to 'wear' an external medical device 24 hours, before introducing such system.[9] Taking into consideration all these advantages and disadvantages, a decision to transition from MDI to the insulin pump is taken on an individual basis after a multi-disciplinary team discussion consisting of: Consultant Diabetologist with special interest and training in pump therapy, diabetes specialist nurse and dietician with special interest in diabetes.[5]In the event of system failures, dislodgement, or damage, there is risk of DKA due to the interruption of insulin supply.[8]

According to the National Institute for Health and Care Excellence (NICE) guidelines on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus, published in July 2008; the pump is only funded in type 1 diabetic patients above the age of 12 years who are unable to reach their target Hba1c level despite optimal care or where increase in doses is difficult in view of multiple hypoglycaemic events. In younger children the pump would only be recommended when insulin administration via multiple daily insulin injections (MDI) is deemed inappropriate or inconvenient, and with the expectation that at some point after the age of 12 years and before adulthood they are given a trial of MDI.[11]

In the Standards of Medical Care in Diabetes published by the American Diabetes Association (ADA) in 2022, the recommendation was that automated insulin pumps should be offered to youths, ideally above the age of 15 years, and adults with type 1 diabetes. Where deemed safe to use, such devices were also recommended in other types of diabetes where insulin deficiency is the aetiology.[8]

In a Danish cross-sectional survey consisting of 770 type 1 diabetic patients above the age of 18 years using the insulin pump, it was found that better Hba1c outcomes were obtained in patients who had achieved higher levels of education. A decrease of 0.4% in Hba1c was noted in those progressing to higher education as opposed to those leaving school after primary education.[12] In the case of system failures, dislodgement or damage, there is risk of DKA as insulin supply gets interrupted.[8]

Patient satisfaction and a positive attitude towards the insulin pump was noted as well in the Italian cross-sectional study conducted between February and August 2021 where out of the 182 type 1 diabetic patients interviewed, 83 were using the continuous subcutaneous insulin pump. This was linked to the fact that such patients had an overall positive attitude when it came to the technology itself, as technology-related stress has been shown to be associated with poorer treatment outcomes and compliance.[13]

In a Swedish study published in 2016 on the Journal of Diabetes Science and Technology, data from the Swedish National Diabetes Register between 1st June 2014 and 16th November 2015 revealed that 8799 out of 35725 type 1 diabetic patients included in the study were using a continuous subcutaneous insulin infusion. The majority of these were females with an average age of 41.5 year old. This study then looked at Hba1c difference and albuminuria in patients on continuous subcutaneous insulin infusion when compared to those with MDI – taking also into consideration the reason why the former cohort were started on the pump. The vast majority of patients using the insulin pump had lower Hba1c when compared to patients on MDI. This however wasn't true in those patients where the insulin pump was initially indicated for poor glycaemic control with a high Hba1c. With regards to albuminuria, although it was found that patients using the insulin pump had a higher incidence of albuminuria, this was again linked

with the fact that such patients might have switched to the pump from the MDI regime in view of previously poor glycaemic control, hence already leading to end organ damage and albuminuria.[14]

In the multicentre randomised control trial – SCIPI RCT published in 2018 on Health Technology Assessment, data from children and young people (aged 7 months to 15 years) started on either a continuous subcutaneous insulin infusion or MDI at diagnosis of type 1 diabetes were compared to each other. This study concluded that overall there was no noted advantage of the insulin pump compared to the MDI in the first year from diagnosis of type 1 diabetes. Also, the insulin pump was not a cost-effective treatment in this particular group of patients. These conclusions were based on the fact that Hba1c levels between the two groups were not significantly different when checked 1 year after start of treatment. Despite these findings, it did show however a better quality of life described especially by parents of such patients.[14] These finding correlate to the recommendations of both the National Institute for Health and Care Excellence (NICE) and the American Diabetes Association (ADA) guidelines with regards to age when insulin pumps should be ideally used.[8,11]

In the review by Bassi et al published in March 2023, different Automated Insulin Delivery (AID) systems available for clinical use were researched to look at their individual features and overall clinical benefit for type 1 diabetic patients. Such systems studied included the Minimed 780G, which was the first hybrid closed loop system launched by the pharmaceutical industry in 2016, and Tandem Control-IQ amongst others. Overall, all the systems have shown an improved glycaemic control manifested by increased time in range, decreased time below range (hypoglycaemic events), as well as a decrease in Hba1c levels.[4]

Having better glycaemic control reflects on long-term morbidity and mortality. A Swedish study by Steineck, et al published on the BMJ in 2015 compared the incidence of cardiovascular disease and mortality in type 1 diabetic patients on MDI versus those on insulin pumps. Out of the 18168 people studied, 2441 were on the insulin pump, while the rest were on MDI. Such patients were then followed-up for a mean of 6.8 years. With regards to all outcomes studied (including both non-fatal and fatal coronary heart and cardiovascular diseases), patients on the insulin pump had a lower hazard ratio when compared to those on MDI. It was however difficult to conclude whether these findings were related to any possible clinical or educational factors linked to the insulin pump or the physiology how the insulin pump works.[16]

Other studied diabetes-related morbidities included retinopathy and peripheral neuropathy. In a prospective study from the years 2000 to 2014, 989 adolescent patients between the ages of 12 and 20 years that had at least received 12 months of treatment with either the insulin pump or MDI, were studied. Although no statistically significant difference was noted among the two groups when it came to Hba1c levels, patients on the insulin pump showed a lesser incidence of retinopathy and peripheral neuropathy when compared to the MDI.[17]

Not only has the insulin pump been shown superior to the MDI system with regards to reducing long-term micro- and macrovascular complications related to type 1 diabetes, but also when it comes to risk of hypoglycaemia. Without any doubt, hypoglycaemia is one of the most feared complications of diabetes that limits reach of adequate treatment targets. From the 21 studies analysed during the meta-analysis by Pickup and Sutton, they concluded that severe hypoglycaemic events were related more to MDI use and this was more prevalent in adults who had been diagnosed with diabetes for a longer time.[18] In the evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycaemia, published on Diabetes Care in 2015, it was recommended that the sensor-augmented insulin pump is a good option apart from patient education, continuous glucose monitoring and pancreatic islet cell transplantation, to prevent severe hypoglycaemia events. In fact the insulin pump was recommended at stage 2 in the proposed treatment algorithm for type 1 diabetes when faced with challenges of hypoglycaemia.[19]

Apart from a decrease in severe hypoglycaemic events, in the PR-IAH study (protective and risk factors of impaired awareness of hypoglycaemia in patients with type 1 diabetes), published in 2023, the insulin pump was found to be related to less impaired awareness of hypoglycaemia.[20] Also, in the pilot study by Giménez et al, it was shown that after 2 years from starting the insulin pump, there was a noted improvement in patient hypoglycaemia unawareness when compared to patients with MDI.[21]

The use of the insulin pump is also being studied for use in type 2 diabetes especially in around 30% of these patients who are not able to reach their glycaemic targets even with insulin in the form of MDI.[22,23] Hba1c amelioration was even observed in

type 2 diabetic patients on the pump when compared to those on MDI. In the OpT2mise randomised open-label controlled trial, 331 type 2 diabetic patients were randomised in such a way that 168 patients were started on the insulin pump, while the rest were given MDI. At the end of the 6 months of this study, patients on the insulin pump required less insulin in a day with a mean of 97 units when compared to a mean of 122 units in those patients treated with MDI.[24]

When it came to quality of life, similarly to patterns seen in type 1 diabetic patients on the pump, patients with type 2 diabetes were also shown to have an improved quality of life. With regards to expense, although initial costs to start and maintain an insulin pump are higher when compared to MDI, in the long term, costs are less when compared to those involved in morbidity management related to poor glycaemic control.[23,24]

The technology of the insulin pumps has greatly evolved over the years since the first model of the continuous subcutaneous insulin infusion in 1976. The year 2005 saw the introduction of sensor augmented pumps, with a later on added feature of low glucose suspend to stop the pump whenever low blood sugar was detected. In 2009, the patch pump which excluded the need for tubing was introduced. Then, the current most modern technology available since 2019 was that of the AHCL. The way this works is by combining prandial boluses of insulin which are administered, in conjunction to the continuous basal insulin infusion – the latter rate being controlled by continuous blood glucose monitoring incorporated to the system. Such systems promote a more flexible lifestyle and therefore are better accepted especially when it comes to adolescents and young adults.[4,25]

The bihormonal artificial pancreas (BIHAP), or bionic pancreas, consists of a wearable device which unlike the insulin pump, consists of both insulin as well as glucagon as the hormones that can be potentially delivered to the patient. The concept of closed-loop systems making use of both insulin and glucagon has been around at least since the 1960s where a researcher – Kadish had mentioned the use of both hormones in his work. The advantage of having glucagon alongside insulin incorporated in the pump is that of a lesser incidence of hypoglycaemic events when compared to pumps delivering insulin alone. .[26] An added advantage of the BIHAP is that, in combination with continuous glucose monitoring, it is able to regulate glucose control via the release of insulin and/or glucagon without the need for the patient to input data such as mealtimes and time of physical activity. Therefore, it increases the independence of type 1 diabetic patients as the system automatically delivers hormones in response to glucose-sensing mechanisms without the need for carbohydrate counting, etc.[27]

In the multicentre, prospective, single-arm trial in the Netherlands by Van Bon et al, adults with type 1 diabetes from eight hospitals in the Netherlands were enrolled for this one year trial. 90 type 1 diabetic patients between the ages of 18 and 75 years who had already been using the continuous blood glucose monitor (CGM) for at least three months were assessed for eligibility to participate in trial. Of these 82 were eventually enrolled and finally 71 completed the trial up to the end of the one-year period. Blood glucose data was collected from the patients continuous blood glucose monitors (CGMs) starting 4 weeks before the participants were started on bihormonal pumps, and then patients were monitored three-monthly. Data collected included: time in range (TIR), daily insulin and glucagon use amongst others. Mean TIR achieved at the end of the trial was that of 80.3%, which is better when compared to the 67.0-73.6% of the hybrid closed loop systems (consisting of insulin only). What was also noted is that total daily insulin administered increased by at least three units, while when it came to glucagon administration, this amounted to less than 1mg daily.[27] In the 13-week multicentre randomised trial by the Bionic Pancreas Research Group published in The New England Journal of Medicine September 2022 edition, the positive results of a better Hba1c levels were again reiterated when compared to the standard care of MDI.[25]

At present, the only bionic pancreas approved by the FDA in the United States is the iLET bionic pancreas developed by Beta Bionics. This technology has been available for patient use since 2023.[28]

Treatment advances alone are only a part in the success story of the management of diabetes – particularly type 1 diabetes. The introduction CGM in 1999 has brought with it greater independence in the life of such patients (irrespective of whether this is paired with an insulin pump or not). The continuous glucose monitor consists of a device with a subcutaneous needle that is worn by the patient and it monitors the blood glucose continuously and then transmitting the collected date either to an app on the patient's smartphone or to a handheld reading device purchased with the monitor. There are currently two systems by which this data can be transferred. Either real-time continuous glucose monitoring (rtCGM) or flash CGM, whereby in the

latter case, the sensor attached to the patient needs to be manually scanned with the reader. Such systems have the ability to issue alarms so that the patient is made aware when the blood glucose is either too low or too high. Finally, the CGM technology in certain cases can also allow the patient's Diabetologist to remotely access blood glucose readings, allowing for the possibility of telemedicine and modernising the approach towards patient care [29]

CONCLUSION

The management of diabetes has greatly evolved over the years, especially when it comes to type 1 diabetes, where such a diagnosis meant premature death before the early 1920s. Despite being a 100-year old drug, insulin kept evolving to meet its clinical needs for better patient outcome. Not only different forms of insulin have been developed but also the way insulin is administered has changed. Compared to early days, less volumes are required and these can be administered in a safer and less uncomfortable way for the patient. The two main forms of insulin administration available at present are the MDI and the insulin pump. The latter became available in the 1970s and is still developing coming up with newer systems in combination with CGM to mimic the function of the pancreas.

Several studies done have proved that insulin pump users showed better Hba1c outcomes, resulting in less long-term micro- and macrovascular complications. Also, less hypoglycaemic events were reported, leading to a better quality of life and patient satisfaction. These patterns were also observed in studies done in type 2 diabetic patients with the insulin pump – hence showing promising results for future use of such technology in this cohort of patients.

REFERENCES

1. Lewis GF, Brubaker PL. The discovery of insulin revisited: lessons for the modern era. J Clin Invest. 2021;131.(1)
2. Secrest AM, Washington RE, Orchard TJ. Chapter 35: Mortality in Type 1 Diabetes. Diabetes in America. 3rd ed. 2014.
3. Kesavadev J, Saboo B, Krishna MB, Krishnan G. Evolution of insulin delivery devices: from syringes, pens, and pumps to DIY artificial pancreas. Diabetes Ther. 2020;11:1251-69.
4. Bassi M, Franzone D, Dufour F, et al Automated insulin delivery systems: use and efficacy in children and adults with type 1 diabetes and other forms of diabetes in Europe in early Life. 2023;13:783.
5. Wilmot E, Hammond P. Best practice guide: continuous subcutaneous insulin infusion (CSII) – a clinical guide for adult diabetes services. 2018.
6. Najjar SM, Perdomo G. Hepatic insulin clearance: mechanism and physiology. Physiology (Bethesda). 2019;34:(3)198-215.
7. Aleppo G, Vohnoutka E, Eytan S. Insulin pump essentials. 2023.
8. Draznin B, Aroda VR, Bakris G, et al Diabetes technology: standards of medical care in diabetes. Diabetes Care. 2022;45:(1)97-112.
9. Berget C, Messer LH, Forlenza GP. A clinical overview of insulin pump therapy for the management of diabetes: past, present, and future of intensive therapy. Diabetes Spectr. 2019;32:(3)194-204.
10. Diabetes.co.uk. Cost of insulin pumps. 2019.
11. NICE. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. Technology appraisal guidance. 2008.
12. Schmidt S, Madsen KP, Bjergaard UP, et al Associations between clinical and psychosocial factors and HbA1c in adult insulin pump users with type 1 diabetes. Acta Diabetol. 2023;60:(8)1089-97.

13. Messina R, Indelicato L, Iommi M, et al Assessing attitudes towards insulin pump therapy in adults with type 1 diabetes: Italian validation of the Insulin Pump Attitudes Questionnaire. Acta Diabetol. 2023;60:(5)687-95.
14. Jendle JH, Rawshani A, Svensson AM, Avdic T, Gudbjörnsdóttir S. Indications for insulin pump therapy in type 1 diabetes and associations with glycaemic control. J Diabetes Sci Technol. 2016;10:(5)1027-33.
15. Blair J, McKay A, Ridyard C, et al Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT. Health Technol Assess. 2018;22.(42)
16. Steineck I, Cederholm J, Eliasson B, et al Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18168 people with type 1 diabetes: observational study. BMJ. 2015;350:h3234.
17. Zabeen B, Craig ME, Virk SA, et al Insulin pump therapy is associated with lower rates of retinopathy and peripheral nerve abnormality. PLoS One. 2016;11.(4)
18. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008;25:(7)765-74.
19. Choudhary P, Rickels MR, Senior PA, et al Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. Diabetes Care. 2015;38:1016-29.
20. Sakane N, Kato K, Hata S, et al Protective and risk factors of impaired awareness of hypoglycemia in patients with type 1 diabetes: a cross-sectional analysis of baseline data from the PR-IAH study. Diabetol Metab Syndr. 2023;15:79.
21. Giménez M, Lara M, Conget I. Sustained efficacy of continuous subcutaneous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycemia and hypoglycemia unawareness: a pilot study. Diabetes Technol Ther. 2010;12:517-21.
22. Jendle J, Reznik Y. Use of insulin pumps and closed-loop systems among people living with diabetes: a narrative review of clinical and cost-effectiveness. Diabetes Obes Metab. 2023;1-12.
23. Roze S, Duteil E, Smith-Palmer J, et al Cost-effectiveness of continuous subcutaneous insulin infusion in people with type 2 diabetes in the Netherlands. J Med Econ. 2016;19:(8)742-9.
24. Reznik Y, Cohen O, Aronson R, et al Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet. 2014;384(9950):1265-72.
25. Russell SJ, Beck RW, Damiano ER, et al Multicenter, randomized trial of a bionic pancreas in type 1 diabetes. N Engl J Med. 2022;387:(13)1161-72.
26. Pickup JC, Khan F, Zhi ZL. Chapter 12: Bionic pancreas. In: Chawla R, editor. Recent Advances in Diabetes. New Delhi: Jaypee Brothers Medical Publishers; p. 129-34.
27. Van Bon AC, Blauw H, Jansen TJP, et al Bihormonal fully closed-loop system for the treatment of type 1 diabetes: a real-world multicentre, prospective, single-arm trial in the Netherlands. Lancet. 2024;6:(4)272-80.
28. Diabetes UK. Life-changing 'bionic pancreas' for type 1 diabetes available in the US. https://www.diabetes.org.uk/about-us/news-and-views/life-changing-bionic-pancreas-type-1-diabetes-available-us. Accessed 11 May 2025
29. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. Diabetes Metab Syndr. 2018;12:(2)181-7.