Continuous subcutaneous insulin infusion: a local perspective

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This article was published on 16 Aug 2023 at www.hkmj.org.

Hong Kong Med J 2023;29:337–41
https://doi.org/10.12809/hkmj219644

Introduction

Intensive treatment of diabetes mellitus (DM) improves short-term well-being while mitigating micro- and macrovascular complications,[1,2] but it can be associated with a three-fold increase in the risk of severe hypoglycaemia (61.2 vs 18.7 cases per 100 patient-years) as well as weight gain.[1] Intensive treatment of type 1 diabetes mellitus (T1DM) involves multiple daily injection (MDI) insulin therapy or continuous subcutaneous insulin infusion (CSII) therapy. During the T1DM Diabetes Control and Complications Trial (DCCT), over a mean intervention period of 6.5 years, intensive treatment with MDI insulin therapy or CSII therapy (using less sophisticated pumps that lacked modern continuous glucose monitoring [CGM] technology to measure glucose levels in interstitial fluid) yielded a mean glycated haemoglobin (HbA1c) level of 7.2% (vs 9.1% for the conventional therapy group with one or two daily insulin injections) and reductions of 26% to 76% in microvascular complications.[1] The observational Epidemiology of Diabetes Interventions and Complications study continued to follow DCCT participants, with all participants being recommended intensive diabetes management and returned to their usual healthcare team. In both DCCT treatment arms, HbA1c levels converged at around 8.1%; sustained reductions in micro- and macrovascular complications were observed in the prior intensive treatment group over 18 years of follow-up.[2,3]

Severe hypoglycaemia risk is strongly associated with HbA1c level, with a 13% to 15% increase in such risk for every 10% decrease in HbA1c level.[3] Newer forms of insulin, modern pumps, and CGM technology have led to substantial decreases in hypoglycaemia, including severe hypoglycaemia.[4] For instance, CSII technology has considerably advanced over the past two decades, which allows similar HbA1c levels to be achieved without an increased risk of hypoglycaemia; hybrid closed loop (HCL) pumps have also become commercially available.

This article provides an overview of insulin pump therapy, evidence concerning its clinical efficacy, its limitations, and local challenges in Hong Kong.

History and evolution of insulin pumps

The first pump prototype, developed in the 1960s, was a heavy machine worn as a backpack. Early pumps had suboptimal characteristics (eg, quality control, battery power, and dosing flexibility), along with technical failures and rigid blockage-prone infusion sets. A modern pump is a battery-powered device that is worn externally and continuously with an internal reservoir for rapid-acting insulin (100 IU in strength), which is subcutaneously delivered through an infusion set. The reservoir and infusion set are changed by the user or caregivers every few days and batteries are changed every 2 weeks.

Basal insulin is continuously delivered at modifiable infusion rates, or by a control algorithm in advanced CGM-linked HCL pumps; insulin boluses for meals and instances of hyperglycaemia require user input. Continuous subcutaneous insulin infusion therapy offers greater flexibility over MDI insulin therapy; it allows variations in basal infusion rate and the use of temporary basal rates (eg, higher for sedentary periods or illnesses and lower for aerobic exercise), as well as precise insulin delivery, various bolus patterns (for some devices), and lower MDI burden. Essential pump settings are shown in the Table; on HCL pumps in automated mode (see below), adjustable settings are the insulin-to-carbohydrate ratio and active insulin time.

Standalone (non-HCL) pumps solely deliver insulin; users measure blood and/or interstitial fluid glucose level (by CGM systems) to help determine appropriate insulin doses. Continuous glucose monitoring tracks interstitial fluid glucose level for 7 to 14 days; it provides optional alarms for hyperglycaemia and hypoglycaemia. The United

TABLE. Essential settings in an insulin pump

Parameter	Setting
Basal rate	Amount of basal insulin programmed for delivery at a uniform rate each hour
Insulin-to-carbohydrate ratio	Amount of carbohydrates (in g) covered by one unit of insulin
Insulin sensitivity factor	Amount of glucose reduction (in mg/dL or mmol/L) from one unit of insulin
Blood glucose target	Blood glucose target used in bolus calculations by insulin pump
Active insulin time	Length of time the bolus calculator software tracks active insulin after a bolus is administered

States Food and Drug Administration–approved CGM systems available in Hong Kong include Abbott's FreeStyle Libre, Dexcom, and Medtronic's MiniMed systems.

The most advanced commercial pumps are HCL pumps. The first HCL pump, the Medtronic MiniMed 670G, was approved by the United States Food and Drug Administration in 2016 for people with T1DM aged ≥7 years[5]; it became available in Hong Kong in 2019. Hybrid closed loop pumps use a built-in computer algorithm with learning capabilities to modify basal insulin delivery in response to CGM measurements. Algorithm-based automatic adjustments are made at 5-minute intervals according to the current sensor glucose value, the extent and duration of deviation from the glucose target, the speed of changes in glucose level, and the amount of insulin already delivered. The pumps can function in two modes: manual and automated mode. In automated mode, the Medtronic SmartGuard algorithm in MiniMed 670G adjusts basal insulin to a glucose target of 6.7 mmol/L, or to a user- or caregiver-initiated higher temporary target (eg, 8.3 mmol/L for exercise). The pumps function in manual mode if CGM data are unavailable or if glucose reading or insulin delivery rate is persistently high.

Pump data can be uploaded to a cloud-based programme, which can be accessed (with patient permission) by the diabetes care team. Uploaded report analytics include device usage duration; glucose levels, trends, and variability; comparisons of pre- and postprandial glucose levels; estimated HbA1c level; pump settings; and suggestions to improve glycaemic control.

Newer commercial HCL pumps include the Medtronic MiniMed 770G and 780G as well as the t:slim X2/Dexcom G6 CGM system/Control-IQ algorithm. Advances include optional lower glucose targets (eg, 5.7, 6.1 or 6.7 mmol/L), better algorithms, Bluetooth functionality, a smartphone application for pump control, and wireless data uploads that enable others to remotely monitor the wearer's glucose levels.

Clinical efficacy

Continuous subcutaneous insulin infusion therapy lowers HbA1c level, mitigates hyper- and hypoglycaemia, improves quality of life, reduces chronic complications, and—particularly when using sensor-augmented pumps—increases time in range (TIR) and decreases glucose variability. A meta-analysis of trials from 2008 to 2015 showed that CSII therapy reduced HbA1c level by 0.37% (95% confidence interval [CI]=0.24-0.51) compared with MDI insulin therapy; it also reduced the incidence of nocturnal hypoglycaemia.[6] However, the included trials had a moderate to high risk of bias related to funding sources, considerable loss to follow-up, and lack of or unclear descriptions of concealment and masking. In most studies, a higher HbA1c level before pump initiation was associated with greater glycaemic improvement.[7,8] Sensor-augmented pumps reduced severe hypoglycaemia, frequent hypoglycaemic episodes, and nocturnal hypoglycaemia in adults and children with T1DM, with no change or worsening of HbA1c level.[9] A Swedish National Diabetes Register–based observational study of people with T1DM (n=18 168, including 2441 CSII users; mean follow-up interval, 6.8 years) demonstrated lower cardiovascular mortality in CSII users than in MDI insulin therapy users, despite similar mean HbA1c levels.[9] Adjusted hazard ratios for CSII therapy were significantly lower: 0.55 (95% CI=0.36-0.83) for fatal coronary heart disease, 0.58 (95% CI=0.40-0.85) for fatal cardiovascular disease (coronary heart disease or stroke), and 0.73 (95% CI=0.58-0.92) for all-cause mortality.

For decades, HbA1c has been regarded as the main indicator of glycaemic control in clinical and research settings.[10,11] An important limitation of HbA1c is its poor responsiveness to hypoglycaemia. Glycaemic variability is a risk factor for hypoglycaemia, hyperglycaemia, and chronic complications; it can also be used as an indicator during treatment optimisation. Regardless of mean HbA1c level, higher glycaemic variability is associated with an increased risk of adverse DM outcomes,[12] including chronic complications and mortality. In clinical management of people with T1DM, CSII therapy is associated with lower glycaemic variability, compared with MDI insulin therapy.[13,14]

The Medtronic MiniMed 670G is safe and effective in the treatment of T1DM; it increases TIR, lowers HbA1c level, and mitigates hyperglycaemia/hypoglycaemia without increasing the rates of severe hypoglycaemia or diabetic ketoacidosis.[15] In a pivotal trial, the use of an HCL system significantly reduced

HbA1c level compared with a sensor-augmented pump (HCL: 8.3% to 7.4% vs sensor-augmented pump: 8.2% to 7.7%), with longer TIR and shorter hypoglycaemia duration.[16] The first randomised trial of the Medtronic MiniMed 670G HCL pump in adults was completed by our Australian colleagues.[17] Participants were randomised to 6 months of HCL pump use (n=61) or the control group that consisted of ongoing MDI insulin therapy or standard pump use (without CGM) with access to a glucose meter and insulin bolus calculator (n=59). The primary outcome was a TIR of 70 to 180 mg/dL by masked CGM during the final 3 weeks. Hybrid closed loop pump use was associated with significant improvements in all glucose metrics, leading to 3.6 additional hours of TIR per day. Such use also improved diabetes-specific well-being; no participants exhibited worsened sleep quality, diabetes-related distress or cognition. Various studies have consistently demonstrated a 6% to 11% increase in TIR during HCL pump use, compared with MDI insulin therapy.[15,16,18-20] Subsequent real-world data have been similar to clinical trial results.[21,22]

Limitations

Continuous subcutaneous insulin infusion therapy increases flexibility regarding mealtimes, carbohydrate intake, and physical activity; however, it increases costs, time, and educational burden for clinicians and users.

Patient selection for CSII therapy involves consideration of HbA1c level, DM complications, vision, numeracy, problem-solving skills, psychological status, hypoglycaemia awareness, prior adherence to diabetes self-care and follow-up, expectations, and ability to afford pump therapy. A supportive multidisciplinary team is needed: an endocrinologist familiar with CSII therapy, a diabetes educator, a dietitian, and a representative from the device company. Patient responsibilities include regular self-monitoring of glucose, possible CGM calibration, reliable carbohydrate counting and bolusing, uploading pump data (unless automated), and responding to pump alerts.

Potential skin and infusion set issues include set dislodgement, occlusion, pump malfunction, infusion site infection, site scarring, lipohypertrophy, and lipoatrophy. The pump delivers rapid-acting insulin and does not provide background long-acting insulin (eg, in MDI insulin therapy). Thus, no insulin is delivered if the pump is disconnected or malfunctions; if alerts are ignored, diabetic ketoacidosis can occur. Accordingly, relevant education, an alternative insulin delivery method (eg, syringe or pen), and ketone-testing supplies (preferably for blood samples) are key considerations. Cost, privacy, and constant hardware attachment may impact patient preferences.

Glycaemic control is a key driver of patient preference for CSII therapy.[23] Less glycaemic variability, shorter hypoglycaemia duration, and fewer chronic complications are moderately important to users; these factors had similar ratings relative to components of treatment burden, including device size and appearance, cost, ease of use, and embarrassment related to public use. Hybrid closed loop pumps provide reassurance to some patients, along with reduced anxiety, improved sleep, improved confidence, and 'time off' from diabetes demands.[24] Pump discontinuation is uncommon; temporary pump holidays may occur (eg, during a beach vacation). In a longitudinal study (n=8935), pump discontinuation rates were 3% (all ages), 4% (adolescents), and 1% (older adults). Participants who discontinued pump use had a higher baseline HbA1c level. Reasons for discontinuation included problems with wearability (57%), pump-related discomfort or anxiety (44%), and problems with glycaemic control (30%).[25]

Insulin pumps in Hong Kong

In Hong Kong, between 2002 and 2015, T1DM incidence increased from 3.5 (95% CI=2.2-4.9) to 5.3 (95% CI=3.4-7.1) cases per 100 000 person-years in boys and from 4.3 (95% CI=2.7-5.8) to 6.4 (95% CI=4.3-8.4) cases per 100 000 person-years in girls. Among people aged ≥20 years, T1DM incidence remained stable.[26]

The public healthcare system in Hong Kong provides support for approximately 2500 patients with T1DM,[26] including around 100 CSII users. In contrast, 10% to 50% of adults with T1DM and >50% of children with T1DM receive CSII therapy in many Western countries.[27-32] Factors affecting CSII therapy uptake include treatment cost and reimbursement schemes, availability of standardised criteria or clinical recommendations concerning CSII therapy, availability of a multidisciplinary team and trained staff, resources and workload, and patient awareness of CSII therapy benefits and willingness to use the technology.

Additionally, many patients are not educated about pumps, nor are they prepared to invest the necessary time and effort to use a pump. Clinicians may also lack CSII experience (eg, troubleshooting and report interpretation) and have no time to gain appropriate experience.[33] Only several Hong Kong endocrinologists have undergone extensive training in the use of pumps and CGM at leading centres in Australia and other countries. Cost remains an issue in Hong Kong—pumps, CGM, and associated expenses are not subsidised by the government or most health insurance schemes. A Swedish National Diabetes Register–based study showed that the mean annual cost was approximately US$4000 higher for CSII therapy than for MDI insulin therapy.[32]

Future directions

Hybrid closed loop pumps represent a step towards the 'artificial pancreas', although this term is suboptimal because current systems only deliver insulin (ie, no other hormones or pancreatic exocrine functions). Closed-loop research is rapidly advancing. An 'ideal' pump would automatically and accurately deliver insulin with a very rapid onset and offset (with or without hormones such as glucagon[34]) to maintain normal blood glucose level in various situations. It would also include a compact pump with minimal attached hardware, reliable calibration-free CGM (now available) and movement monitoring (to adjust for exercise), and other analytes (eg, ketones and lactate). Finally, it would be user-friendly, efficient, cost-effective, and affordable for both healthcare systems and individuals.

In patients with T1DM, glucagon secretion is also impaired. A bihormonal pump combining insulin and glucagon infusions is feasible for hypoglycaemia management; research has shown improvements in glycaemic control compared with insulin pump use alone.[34,35] However, device complexity remains a limitation because of the short duration of glucagon stability and enhancement of insulin resistance during chronic glucagon administration.

Hybrid closed loop and emerging closed-loop pumps are important technological advances in life-saving and life-easing insulin treatment. Greater availability and access to this technology can improve glycaemic control and quality of life for people with T1DM in Hong Kong. These improvements will require reimbursement from the government and health insurance schemes, along with medical expertise, structured care during pump therapy, and better awareness of CSII therapy and its benefits.

Author contributions

Concept or design: TTL Yau, AJ Jenkins.
Acquisition of data: TTL Yau.
Analysis or interpretation of data: TTL Yau.
Drafting of the manuscript: TTL Yau.
Critical revision of the manuscript for important intellectual content: AJ Jenkins, RCW Ma.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

TTL Yau has disclosed no conflicts of interest. AJ Jenkins has been on advisory boards for Medtronic, Sanofi, and Abbott, and has received pump- and sensor-related research grant support from Medtronic, Sanofi, Abbott, Juvenile Diabetes Research Foundation, and The Helmsley Charitable Trust. RCW Ma has received research support from Bayer, Novo Nordisk, Roche Diagnostics (Hong Kong) Limited, Sanofi, as well as consultancy or speaker fees from Bayer, Merck, and Medtronic, all of which has been donated to support diabetes research at The Chinese University of Hong Kong.

Acknowledgement

TTL Yau thanks the training and experience provided by the diabetes unit clinicians of Royal North Shore Hospital (Sydney), Royal Prince Alfred Hospital (Sydney), St Vincent's Hospital (Melbourne), and Ms Kerryn Roem, a practising dietitian in Melbourne, during her period of training in Australia. RCW Ma acknowledges financial support from a Croucher Foundation Senior Medical Research Fellowship.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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