Continuous glucose monitoring and external insulin pump: towards a subcutaneous closed loop

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SUMMARY

The development of an artificial pancreas for the treatment of type 1 diabetes is a highly desired endeavour for type 1 diabetic patients, physicians, scientists and engineers. The development of the first miniaturized external pumps in the 70s and the pharmacokinetic properties of short acting insulin analogues, closer to physiology, have raised hopes for the elaboration of such a device. Recent technological progress in the development of continuous glucose sensors, have improved the reliability and accuracy of these devices. This has led to the development of prototypes of closed-loop system based on the combination of a continuous monitor, a control algorithm, and an insulin pump. This review focuses on the SC-SC approach, employing subcutaneous glucose monitoring and subcutaneous insulin delivery. The feasibility of this solution has been proven at a small scale, but remains to be confirmed in the home setting. Intermediate solutions, such as semi-automatic systems, might be immediately valuable.

Key-words: Type 1 diabetes • Continuous glucose monitoring • Continuous subcutaneous insulin infusion • Artificial pancreas • Automated insulin delivery • Review.

RÉSUMÉ

Surveillance glycémique continue et pompe à insuline externe : vers une boucle fermée sous-cutanée

Le développement d'un pancréas artificiel est un objectif hautement désirable pour les patients diabétiques de type 1, les médecins, les scientifiques et les ingénieurs. La mise au point des premières pompes externes miniaturisées dans les années 70, et les propriétés pharmacocinétiques des analogues de l'insuline de durée d'action brève, plus proche de la physiologie, ont suscité des espoirs pour l'élaboration d'un tel outil. Les progrès technologiques récents dans le développement des capteurs de glucose ont amélioré leur sûreté et leur précision. Ceci a permis l'élaboration de prototypes de systèmes en boucle fermée fondés sur la combinaison d'un moniteur continu de glucose, d'un algorithme de contrôle et d'une pompe à insuline. Cette revue est centrée sur l'approche SC-SC, qui utilise la mesure sous-cutanée du glucose et l'administration sous-cutanée de l'insuline. La faisabilité de cette démarche a été prouvée à petite échelle, mais reste à démontrer en ambulatoire. Des solutions intermédiaires, telles que les systèmes semi-automatiques, pourraient présenter un intérêt immédiat.

Mots-clés : Diabète de type 1 • Mesure continue du glucose • Perfusion sous-cutanée continue d'insuline • Pancréas artificiel • Administration automatisée d'insuline • Revue générale.

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The goal of type 1 diabetes treatment is to achieve tight glucose control, in order to avoid chronic complications, while limiting the frequency of hypoglycaemic episodes in the day-to-day life. Although considerable efforts have been made to improve the pharmacokinetics of insulin and to develop user-friendly monitoring and treatment tools, this goal remains difficult to achieve, and the desire and demand for an automated artificial pancreas is still up to date. Such a system includes an insulin pump, capable of delivering insulin continuously, a monitoring device, capable of sensing continuously glucose, and algorithms for calculating the insulin delivery rate, in order to achieve the normalisation of glucose concentrations [1].

Several control algorithms have been proposed for the automated regulation of glucose by insulin. The pioneering device, the Biostator, was developed in the 1970's [2]. However, the use of this bulky device remains limited to hospitals and research centres.

In the last decades, considerable technological progress has been made. Since the introduction of continuous subcutaneous insulin infusion, the insulin pumps have been miniaturised and their reliability improved. The accuracy and reliability of glucose sensing devices has also been improved. It is then tempting to develop a closed-loop system based on these two devices, despite the drawbacks of the subcutaneous tissue, i.e. the delays in glucose sensing and in insulin delivery.

The present review focuses on the development of subcutaneous – subcutaneous (SC-SC) closed-loop systems, which adopt the subcutaneous route for both glucose monitoring and insulin delivery. The intravenous– intraperitoneal approach is developed in this issue by E. Renard *et al* [3].

Continuous glucose monitoring

The information obtained with the glucose monitoring system should be accurate, real-time, and continuous (or frequent if intermittent). The glucose sensors that measure glucose concentrations in the interstitial fluid can be non-invasive or minimally invasive. Most non-invasive approaches are carried out using optical glucose sensors. The basic premise of optical glucose sensors is to direct a light beam through the skin and to measure the alterations of the properties of the reflected light. Although this approach seems attractive, the specificity of glucose measurement is poor, because of numerous interferences [4]. The reverse iontophoresis approach (Glucowatch®, Cygnus) allows the measurement of glucose concentration in the interstitial fluid after its transdermal extraction [5]. After a 3-h warm-up period, the device is capable of providing up to three glucose readings per hour for 12 h after a single point calibration with a self blood glucose measurement. However, the measurement result is not immediately available (the time required for sample extraction and analysis is 20 minutes), and the current applied to the skin causes some degree of irritation. The device cannot be used in case of increased sweating, and this is a concern for the detection of hypoglycaemia. For all these reasons, these two approaches are not suitable for the closed-loop.

Minimal-invasive methods are based on the microdialysis or on the use of amperometric enzyme electrodes.

The microdialysis system developed by Menarini (Glucoday®) can be used for three days [6]. The semi-permeable dialysis fibre is inserted into the subcutaneous tissue and perfused with glucose-free isotonic fluid. Due to the concentration gradient, glucose diffuses from the interstitial fluid through the dialysis membrane into the perfusate. The dialysate is pumped to a glucose sensor outside the body where the glucose concentration is measured continuously. A calibration is required once daily. As the glucose sensor is outside the body, no significant signal drift has to be feared. However, the time lag inherent to the technique is a disadvantage. It is related to the length of the tubing and the perfusion flow rate.

The other minimal invasive approach is based on the use of electrodes covered with glucose oxidase and submitted to the application of a potential. The electrode is inserted in the subcutaneous tissue and measures the change in current flow caused by the enzyme-catalyzed production of hydrogene peroxide, which is proportional to the amount of glucose at the site of insertion. The main drawback of this technique is the signal drift induced by the reaction of the subcutaneous tissue to the electrode and the changes in glucose and oxygen diffusion near the electrode. This can be compensated for by frequent recalibrations.

The continuous glucose monitoring system (CGMS®, Medtronic MiniMed) is the first currently available monitoring system based on this technique. It uses a subcutaneously inserted flexible needle sensor containing glucose oxidase, which converts interstitial glucose into a measured electrical current [7]. It requires four calibrations per day, does not display the current glucose concentration measured, but allows retrospective analysis of interstitial glucose readings every 5 minutes for 72 hours. The next generation of the system (Guardian RT®) functions in real time, with hypoglycaemic and hyperglycaemic alarms, and allows extended use by the patient himself [8].

Two other devices based on the glucose electrode technique and capable of displaying glucose measurements in real-time are currently submitted to the FDA approval: the Navigator® system (Abbott) [9] and the Dexcom® system [10].

All these devices have been studied for their reliability, and most of them for their ability to improve glycaemic control (HbA_{1c} and/or frequency of hypoglycaemic episodes) when used in the real life. At present, the non invasive techniques based on spectroscopy and the reverse iontophoresis technique do not fulfil the desirable features of a glucose monitoring system included in a closed-loop. Minimal invasive techniques, microdialysis and glucose electrodes, allow frequent, durable and reliable glucose monitoring, and can

therefore be used for an automated insulin delivery system. Their weaknesses are the delay of glucose measurement and the disparity of interstitial and venous glucose measurement [11], and the need for frequent recalibration.

Continuous insulin delivery

Continuous subcutaneous insulin infusion (CSII) with external insulin pumps was introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in type 1 diabetic patients [12], by means of more physiological insulinisation than that with multiple daily injections (MDI). The exclusive use of soluble, short acting insulin, infused subcutaneously at the same site for 2 or 3 days, reduces the variability of insulin absorption when compared to long acting insulins. CSII allows a wide flexibility of insulin infusion, thanks to the ability of programming several basal rates and adjusting meal boluses when required. Several studies have concluded to the superiority of CSII over MDI in terms of HbA_{1c} [13-16]. In the DCCT (Diabetes Control and Complication Trial), HbA_{1c} levels in the intensive group were significantly lower with CSII than with MDI (-0.2 to -0.4%) [17]. Recent meta-analyses report an overall benefit of CSII over MDI, with a reduction of HbA_{1c} in the range of 0.4 – 0.5% [18, 19].

Several randomised controlled trials have shown that the use of short-acting insulin analogues is more efficient on HbA_{1c} levels than human insulin [20-22], this has been confirmed by a meta-analysis [23]. The pharmacokinetic properties of the analogues are certainly responsible for the improvement in postprandial glucose levels and stability. However, the efficacy of CSII versus MDI therapy has been evaluated only in a limited number of randomised controlled trials in which rapid-acting analogues were used for both regimens, two out of three concluding to a superiority of CSII [24-26]. The pooled analysis of these three studies suggests that CSII is associated with better glycaemic control, particularly in those patients with suboptimal initial control [27].

The subcutaneous route of insulin delivery is easy to use, and recent improvements in terms of reliability of the devices and pharmacokinetics of the insulin analogues allow to consider its use for an automated insulin delivery, although the subcutaneous site introduces additional delays in insulin kinetics not seen with intravenous delivery.

Subcutaneous – subcutaneous closed loop – system

Two major practical solutions of a closed-loop system based on the body interface exist. The IV– IP approach relies on intravenous glucose monitoring and intraperitoneal insulin delivery and is described elsewhere. The developments of the SC– SC approach, which adopts the subcutaneous route for both glucose monitoring and insulin delivery, is discussed here.

Clinical considerations for the use of a SC-SC closed-loop

The SC– SC approach has the advantage of a minimally invasive solution, with the greatest potential to achieve widespread application. On the other hand, the use of the subcutaneous site is responsible for delays in glucose reading and in insulin action that may be difficult to overcome, especially when rapid changes in insulin delivery are needed to compensate for rapid and large glucose levels changes, especially during the meals.

There are several causes explaining these delays. When glucose levels change, there is a lag in the equilibration between the interstitial and plasma glucose that will vary depending on physiologic conditions. Following a glucose load, the interstitial glucose concentration lags behind the blood glucose. On the contrary, following insulin administration, the decline in glucose concentration in the interstitium precedes that in the blood [28]. With microdialysis based systems, there is an additional lag required to transfer the interstitial fluid sample to the glucose sensor [29]. The delayed absorption kinetics of subcutaneously delivered insulin is an additional factor to be taken into account. It may lessen the efficacy of insulin when glucose levels change rapidly after a meal, but also result in an extended postprandial glucose lowering effect, compromising the efficacy of the system. Therefore, the first control systems based on the SC– SC approach will probably be semiclosed-loop systems or hybrid systems, requiring at least a partial manual assistance to the delivery of insulin for meals [30].

System variability

Not only the difficulty to overcome wide glucose fluctuations after the meals can disturb the efficacy of a control system. Even in healthy individuals, insulin sensitivity varies both day-to-day and throughout the day. Diurnal variance can result either from a change in insulin sensitivity per se, or a change in endogenous glucose production. In a type 1 diabetic patient, these changes result in varying basal insulin requirements throughout the day [31]. Insulin requirements for meals of identical carbohydrate content can also vary, depending on the type of carbohydrate and the presence of dietary fat and alcohol. Insulin sensitivity is also modified by physical exercise, in an individual-specific manner. A large number of parameters can influence insulin requirements, and might interfere with the efficacy of a closed-loop insulin delivery algorithm.

Model Predictive Control (MPC)

In this control approach, a mathematical model of the subject's glucose response is derived from one of the many models of the glucoregulatory system [32]. Measured glucose values enter a "parameter optimiser" which estimates individual parameters of the glucoregulatory model. These parameters are used to make individualised predictions of

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glucose excursions, and take into account the estimation of insulin sensitivity. The model predicts how insulin would affect the future glucose profile, and calculates the first insulin delivery value. On the next sample interval, the difference between the measured glucose and the model-predicted values is reassessed, and the optimal insulin delivery profile is calculated. These steps are repeated, improving the predictive accuracy of the model.

The MPC-based system has been studied by the European consortium of partners on the Advanced Insulin Infusion using a Control Loop (ADICOL) since 2000 [33]. The first clinical studies have been performed with an intravenous (IV) sensor with a 15 minutes sample time and subcutaneous delivery of insulin lispro. The following studies were performed with the same IV sensor, but the measurements were delayed by 30 minutes in order to mimic the time lag associated with a subcutaneous sensor. In these two sets of experiments, the MPC system was able to achieve normoglycaemia during fasting conditions while avoiding hypoglycaemia. A progressive and pronounced reduction in the standard deviation of plasma glucose was observed, demonstrating the ability of the algorithm to bring all subjects close to the target. Another experiment was conducted in the fasting and postprandial condition, the prandial bolus being individually determined according to the carbohydrate content of the meal, and the MPC being run for three additional hours after the meal.

All these experiments were conducted with IV glucose sensing. Only 5 subjects could benefit from the MPC system with a subcutaneous sensor, at the end of the program. Nevertheless, the ADICOL project gives an interesting approach to a semi-closed-loop control with subcutaneous insulin delivery.

Physiologic Insulin Delivery system (PID)

The PID system, aims at mimicking the mechanisms by which the beta-cell maintains tight glucose control. The main points are that the beta-cell adapts its secretory response to the individual's underlying insulin sensitivity, and that it adjusts the ratio of first- to second-phase insulin to compensate for a delay in insulin action. The Medtronic MiniMed external PID system [34] includes three terms: proportional, integral and derivative (figure 1). Basal insulin delivery is determined by the slow component (integral). Once the meal begins, the rate of change component (derivative) results in a rapid rise in insulin delivery, and is accompanied by a proportional component (proportional), as glucose rises above a set-point [35]. This third component is equal to zero when glucose is at target concentration. The derivative component counteracts rapid changes and can be considered to reproduce the first phase of insulin secretion. The integral component adapts to changes in insulin sensitivity and links insulin administration to the difference between the ambient and the target glucose.

The closed-loop insulin delivery system developed by Medtronic-MiniMed is composed of a Guardian-type subcutaneous sensor equipped with a transmitter, and transmitting

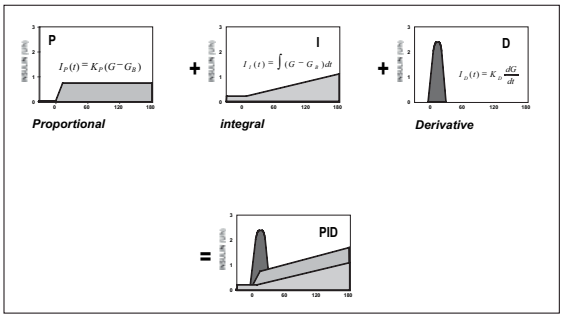

Figure 1
Components of the Physiologic Insulin Delivery (PID) system [adapted from ref. 34].

glucose values to a computer which calculates insulin delivery rates every minute and transmits the rate to an external pump. The first studies with a fully closed-loop were carried out in dogs. The algorithm allowed to reach the glucose target under fasting conditions, but failed to achieve normoglycaemia in the postprandial state [35]. A recent evaluation of the PID system was carried out in 10 type 1 diabetic subjects over 24 hours with meals. Satisfactory glucose control was obtained overnight, but postprandial glycaemic excursions remained excessive. Therefore, a hybrid, semi-automatic control with "priming" conventional pre-meal bolus is currently under investigation in the Yale group.

Conclusion

Glucose monitoring has been the main limiting factor to the development of a viable closed-loop solution, and the perspective of a closed-loop system has been one of the main driving forces for glucose sensor development. The currently available sensors display satisfactory properties in terms of reliability and accuracy. If the subcutaneous route of insulin infusion remains a barrier, the reliability of insulin pumps and the pharmacokinetics of insulin analogues have given adequate answers enough to encourage the hopes for an automated artificial pancreas. Several algorithms are under evaluation, and if the results obtained in the fasting state are more than encouraging, the postprandial state remains difficult to handle with. Before a fully automated device is available, intermediate steps may already be valuable. Continuous glucose monitoring with real-time access to the glucose values, facilitating self-adjustments of diabetes management by the patient, has already proven efficient in pilot studies. Semi-automatic systems, with a partial control of the postprandial state by a manual bolus, are also of interest. The development of closed-loop solutions in controlled environments such as in the intensive care units, is an interesting area, as the benefits of tight control have been proven in this field. From this application area, spin-off to other areas should be possible.

References

1. Jaremko J, Rorstad O. Advances toward the implantable artificial pancreas for treatment of diabetes. Diabetes Care 1998;21:444-50.
2. Clemens AH, Chang PH, Myers RW. The development of Biostator, a glucose-controlled insulin infusion system (GCIIS). Horm Metab Res 1977;7(Suppl):23-33.
3. Renard E, Costalat G, Chevassus H, *et al*. Artificial beta cell: clinical experience toward an implantable closed-loop insulin delivery system. Diabetes Metab 2006;32(Supp.):497-502.
4. Koschinsky T, Heinemann L. Sensors for glucose monitoring: technical and clinical aspects. Diabetes Metab Res Rev 2001;17:113-23.
5. Tamada JA, Garg SK, Jovanovic L, *et al*. Noninvasive glucose monitoring: comprehensive clinical results. Cygnus Research Team. JAMA 1999;282:1839-44.
6. Maran A, Crepaldi C, Tiengo A, *et al*. Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter evaluation. Diabetes Res Clin Pract 2000;50:S333.
7. Mastrototaro JJ. The MiniMed continuous glucose monitoring system. Diabetes Technol Ther 2000;2(suppl 1):S13-S18.
8. Bode B, Gross K, Rikalo N *et al*. Alarms based on real-time sensor glucose values alert patients to hypo-and hyperglycemia: the Guardian continuous monitoring system. Diabetes Technol Ther 2004;6:105-13.
9. Feldman B, Brazg R, Schwartz S, *et al*. A continuous glucose sensor based on wired enzyme technology – results from a 3-day trial in patients with type 1 diabetes. Diabetes Technol Ther 2003;5:769-79.
10. Garg S, Zisser H, Schwartz S *et al*. Improvement in Glycemic Excursions with a Transcutaneous, Real-Time Continuous Glucose Sensor. A randomized controlled trial. Diabetes Care 2006;29:44-50.
11. Rebrin K, Steil GM, Van Antwerp WP, *et al*. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for glucose monitoring. Am J Physiol 1999;277:E561-E571.
12. Pickup JC, Keen H, Parsons JA, *et al*. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. BMJ 1978;1:204-7.
13. Chantelau E, Spraul M, Muhlhauser I, *et al*. Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for type 1 (insulin-dependent) diabetes mellitus: a one centre experience. Diabetologia 1989;32:421-6.
14. Helve E, Koivisto VA, Lehtonen A, *et al*. A crossover comparison of continuous insulin infusion and conventional injection treatment of Type I diabetes. Acta Med Scand 1987;221:385-93.
15. Mecklenburg RS, Benson JW Jr, Becker NM, *et al*. Clinical use of the insulin infusion pump in 100 patients with type I diabetes. N Engl J Med 1982;26:513-8.
16. Ronn B, Mathiesen ER, Vang L, *et al*. Evaluation of insulin pump treatment under routine conditions. Diabetes Res Clin Pract 1987;3:191-6.
17. The Diabetes Control and Complication Trial Research Group. Implementation of treatment protocols in the Diabetes Control and Complication Trial. Diabetes Care 1995;18:361-76.
18. Pickup J, Mattock M, Kerry S. Glycemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2002;324:705-8.
19. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy. A meta-analysis. Diabetes Care 2003;26:1079-87
20. Zinman B, Tildesley H, Chiasson JL, *et al*. Insulin lispro in CSII: results of double-blind cross-over study. Diabetes 1997;46:440-3.
21. Melki V, Renard E, Lassmann-Vague V, *et al*. Improvement of HbA_{1c} and blood glucose stability in IDDM patients treated with Lispro insulin analog in external pumps. Diabetes Care 1998;21:977-82.
22. Renner R, Pfützner A, Trautmann M, *et al*. Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Diabetes Care 1999;22:784-8.
23. Colquitt J, Royle G, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. Diabet Med 2003;20:863-6.
24. Hanaire-Broutin H., Melki V, Bessières-Lacombe S, *et al*. The GEDEC Study Group. Comparison of CSII and MDI regimen using insulin Lispro in type 1 diabetic patients on intensified treatment: a randomized study. Diabetes Care 2000;23:1232-5.
25. De Vries JH, Snoek FJ, Kostense PJ, *et al*. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25:2074-80.
26. Tsui E, Barnie A, Ross L, *et al*. Intensive insulin therapy with insulin lispr: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care 2001;24:1722-7.
27. Retnakaran R, DeVries JH, Hanaire-Broutin H, *et al*. Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections. Modeling predicted benefits in relationship to baseline A1c. Diabetes Care 2005;28:1835-6.
28. Aussedat B, Dupire-Angel M, Gifford R, *et al*. Interstitial glucose concentration and glycemia: implications for continuous subcutaneous glucose monitoring. Am J Physiol Endocrinol Metab 2000;278:E716-E728.
29. Heinemann L. Continuous glucose monitoring by the means of the microdialysis technique: underlying fundamental aspects. Diabetes Technol Ther 2005;5:545-61.
30. Hovorka R. Continuos glucose monitoring and closed-loop systems. Diabetic Medicine 2006;23:1-12.
31. Steil GM, Murray J, Bergman RN, *et al*. Repeatability of insulin sensitivity and glucose effectiveness from the minimal model: implications for study design. Diabetes 1994;43:1365-71.
32. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. Diabetes Technol Ther 2005;7:28-47.
33. Hovorka R, Chassin LJ, Wilinska ME, *et al*. Closing the loop: the Adicol experience. Diabetes Technol Ther 2004;6:307-18.
34. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery – the path to physiological glucose control. Adv Drug Deliv Rev 2004;56:125-44.
35. Steil GM, Saad MF. Automated insulin delivery for type 1 diabetes. Curr Opin Endocrinol Diabetes 2006;13:205-11.