

A Review of the Current Challenges Associated with the Development of an Artificial Pancreas by a Double Subcutaneous Approach

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ABSTRACT

Introduction: Patients with diabetes type 1 (DM1) struggle daily to achieve good glucose control. The last decade has seen a rush of research groups working towards an artificial pancreas (AP) through the application of a double subcutaneous approach, i.e., subcutaneous (SC) continuous glucose monitoring (CGM) and continuous subcutaneous insulin

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infusion. Few have focused on the fundamental limitations of this approach, especially regarding outcome measures beyond time in range.

Methods: Based on insulin physiology, the limitations of CGM, SC insulin absorption, meal challenge, and physical activity in DM1 patients, we discuss the limitations of the double SC approach. Finally, we discuss safety measures and the achievements reported in some recent AP studies that have utilized the double SC approach.

Results: Most studies show that a double SC AP increases the time in range compared to a sensor-augmented insulin pump and shortens the time in hypoglycemia. Despite these achievements, the proportion of time spent in hyperglycemia is still roughly 20–40%, and hypoglycemia is still present 1–4% of the time. The main factors limiting further progress are the latency of SC CGM (at least 5–10 min) and the slow pharmacokinetics of SC-delivered fast-acting insulin. The maximum blood insulin level is reached after 45 min and the maximum glucose-lowering effect is observed after 1.5–2 h, while the glucose-lowering effect lasts for at least 5 h.

Conclusions: Although using a double SC AP leads to significant improvements in glucose control, the SC approach has severe limitations that hamper further progress towards a robust AP.

Keywords: Artificial pancreas; Continuous glucose monitoring; Continuous subcutaneous insulin infusion; Type 1 diabetes

INTRODUCTION

Patients with diabetes mellitus type 1 (DM1) are totally dependent on external insulin to adjust their glucose levels to ensure that they are within the safe range that avoids diabetic ketoacidosis or serious hypoglycemia [1, 2]. Due to the adverse effects of chronically elevated glucose levels, patients with DM1 are further advised to aim for glucose levels that approach the physiologically normal range, but this increases the risk of hypoglycemia in most patients [3–5]. While attempting to shift glucose levels to keep them within the therapeutic range, oscillations between the extremes of hyper- and hypoglycemia are common, even in experienced patients, and some patients do not regain control despite spending significant effort to do so [6, 7]. In many patients, this persistent focus on glucose levels and insulin administration has a major impact on their quality of life, with some ending up on sick leave or drawing a disability pension [8–10]. Severe hypoglycemia is a fearful experience as it can have serious—even life-threatening—consequences [11, 12].

To help patients to achieve optimal glucose control, researchers are constantly hunting for new treatment options and accessory devices. The state of the art treatment for DM1 is continuous subcutaneous insulin infusion (CSII) combined with continuous glucose monitoring (CGM), which makes the patient continuously aware of their current glucose levels and allows them to adjust their insulin delivery accordingly [13]. However, it is still not entirely clear whether the use of CGM enables patients to reduce their glucose levels over the long term, and it is a more costly surveillance method than traditional capillary measurements [14]. In recent years, CGM technology has been incorporated into CSII technology, enabling insulin delivery to be suspended during hypoglycemic

episodes that occur during unawareness or sleep [15, 16]. However, even when this treatment is used, most patients still have glucose levels that are far into the diabetic range.

The dream of an artificial pancreas (AP) for the fully automatic delivery of insulin in patients with DM1 has persisted for decades, starting in the 1970s [17–19]. When the first device for subcutaneous CGM became commercially available in the year 2000, the dream gained new momentum [20]. At present, at least 20 major research groups around the world are working on making the dream of an AP come true [21–37]. Most of these groups concentrate on what can be termed the double subcutaneous (SC) approach, combining SC CGM and CSII into a single device [38]. A double SC approach has the advantage that off-the-shelf technology can be used for CGM and insulin delivery by an insulin pump. However, it is often a major challenge for the control algorithm to maintain glucose levels within the therapeutic range when using this approach. The most recent development in this field is the FDA approval of a double subcutaneous approach using a proportional-integral-derivative (PID) algorithm, where insulin doses are tailored according to the output of the CGM [39–41]. Ideally, a robust (fully automatic) AP controls the administration of insulin such that glucose levels are maintained in the therapeutic range and hypo- and hyperglycemic episodes are avoided without the need for ongoing user input (i.e., announcements of meals/physical activity). Although AP systems based on the double SC approach represent significant progress, this approach has certain limitations that hamper the performance of these systems to such an extent that, in our view, they (or, at least, not those systems based on the technology available in the foreseeable future) cannot maintain glucose levels permanently in the normal or near-normal range, which is required of a robust, fully automatic AP. This paper discusses those physiological and technological limitations and their consequences for the possibility of realizing a robust double SC AP that normalizes or near-normalizes glucose levels in patients with DM1.

METHODS

We performed a PubMed search for recent publications (published between January 2014 and December 31, 2016) regarding closed-loop control in the outpatient setting, using the following search terms: [(Outpatient [Title] or outpatient [Title] or home [Title] or Home [Title] or Free-Living [Title] or free-living [Title] or Free-living [Title] or Camp [Title] or camp [Title] or Safety [Title] or safety [Title]) and (Pancreas [Title] or pancreas [Title] or Closed-Loop [Title] or closed-loop [Title] or Closed-loop [Title]) and (Diabetes [Title] or diabetes [Title] or Insulin [Title] or insulin [Title])]. The results of our search are shown in Tables 1 and 2.

The search retrieved 30 studies, and the articles were screened for whether they contained day-and-night data or day-only data in adolescents/adults with certain glucose ranges during at least five consecutive days of closed-loop control. Secondly, the reference lists of the seven articles containing day and night data were screened to see if we could find any further day and night studies lasting at least five consecutive days in the period of interest, but we found none.

Although this search and screening strategy was far from infallible, we believe that it found most of the studies published during this period that delivered outpatient closed-loop data during the day or both the day and night for at least a five-day period, and we also performed a cross-check with the online database of the Doyle group (<http://thedoylegroup.org/apdatabase/>).

Compliance with Ethics Guidelines This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Progress in the Development of the Double SC Approach

In parallel with the development of an insulin-suspend function, several groups have developed and refined associated algorithms,

some of which are now commonly employed for the double subcutaneous AP approach.

One frequently used algorithm is the proportional-integral-derivative (PID) control method, which is commonly used in industrial applications. It takes into account the deviation from a target glucose value (the proportional term), the past values of the deviation (integral term), and the rate of change in the deviation (the derivative term) [36–39].

The most commonly used algorithm is model predictive control (MPC), which predicts the system's behavior and calculates the optimal insulin infusion (optimal with respect to, for example, the deviation from the target glucose level, the deviation from a target zone, the insulin expenditure, etc.). Some MPC algorithms also take into account factors such as meal/carbohydrate input, variable insulin sensitivity, and recent glucose excursions when tailoring the dose of fast-acting insulin [23, 27–31, 35]. Most MPC algorithms aim to achieve a predefined glucose target, some aim to keep the glucose level within a particular range ("zone MPC"), and some do both.

Most recent studies lasting at least five consecutive days in the outpatient setting have explored overnight glucose control, and most of those studies showed significant improvements in the time spent within either a narrow or wider range of glucose levels (3.9–8.0 or 3.9–10.0 mmol/L, respectively), ranging from 50 to 85%, when using closed-loop control [21, 29–35]; other studies found no difference from open-loop control [36, 37]. In addition, many of these studies showed that less time during the night was spent in hypoglycemia [21, 29–31, 34], while others found that there was no difference in time spent in hypoglycemia from that obtained with open-loop control [30, 32, 33, 36].

In contrast to the many overnight studies that have been performed, only a few studies have explored outpatient closed-loop control during both the day and the night.

Whereas around 85% of the time was spent within the therapeutic range in some of the night-time studies [29, 32], the best achievement in the day-and-night studies was around 75–80% of the time spent in the therapeutic

Table 1 Results of the PubMed search for long-term studies (≥ 5 days) published between 2014 and 2016 on continuous closed-loop versus open-loop control during the day and night in the outpatient setting

Study	Included (N)	HbA1c (%)	Evaluated (N)	Observation period		Physical activity during CL period	CL period	CGM	Algorithm	Defined glucose range (mmol/L)	Time in hypoglycaemia (%)	Time in euglycaemia (%)	Time in hyperglycaemia (%)
				OL	CL								
Leelarathna [35]	21 adults	7.6	17	7 d	7 d	Advised not to drive or to undertake strenuous physical exercise under CL	83.0% of the total time	FreeStyle Navigator; Abbott	Control to range MPC	[3.9, 10]	3.7 CL vs 5.0 OL (ns) [#]	74.5 CL vs 61.8 OL (s) [†]	21.9 CL vs 30.5 OL (s) [†]
Russell ^{ab} [29]	20 adults	7.1	20	5 d	5 d	NR	18–18	G4 Platinum, Dexcom	Control to target MPC	[3.9, 10]	4.1 CL vs 7.3 OL (s)	79.5 CL vs 58.8 OL (s)	16.5 CL vs 33.8 OL (s)
Russell ^{ab} [29]	32 adolescents	8.2	32	5 d	5 d	NR	18–18	G4 Platinum, Dexcom	Control to target MPC	[3.9, 10]	3.1 CL vs 4.9 OL (ns)	75.9 CL vs 64.5 OL (s)	21.0 CL vs 30.6 OL (s)
Ly [†] [36]	21 adults/ adolescents	8.6	10 adults/adolescents in CL and 10 adults/adolescents in OL	6 d	6 d	NR	07–07 (93% of total time during day and night)	4 s sensor CL, Enlite sensor OL, Medtronic	PID	[3.9, 10]	2.1 CL vs 2.4 OL (ns)	69.9 CL vs 73.1 OL (ns)	28.4 CL vs 24.8 OL (ns)
Thabit [30]	33 adults	8.5	32 CL, 33 OL	12 w	12 w	CL not used during physical activity during the initial 2 weeks	00–24 (20.2 h/day) [#]	FreeStyle Navigator, Abbott	Control to range MPC	[3.9, 10]	2.9 CL vs 3.0 OL (s)	67.7 CL vs 56.8 OL (s)	29.2 CL vs 38.9 OL (s)
De Bock [37]	8 adults/ adolescents	7.5	8	5 d	5 d	NR	00–24	Enlite II, MiniLink REAL-time sensor, Medtronic	PID	[4.0, 9.9]	NI	67.6 CL vs 58.7 OL (ns) [#]	NI
Renard [31]	20 adults	8.2	20	1 m	1 m	NR	00–24	G4 Platinum, Dexcom	Control to target MPC	[3.9, 10]	1.9 CL vs 3.2 OL (s)	64.7 CL vs 59.7 OL (s)	33.3 CL vs 37.0 (ns)
Bergental ^{†*} [39]	124 adults/ adolescents	7.4	124	2 w	3 m	NR	87.2% of the total time	Enlite III, Medtronic	PID-IFB	(3.9, 10)	3.3 CL vs 5.9 OL (NS)	72.2 CL vs 66.7 OL (NS)	24.5 CL vs 27.4 OL (NS)

The studies had no restrictions regarding meals

HbA1c values and values for the percentage of time that glucose was within the defined range are reported as mean values unless they are labeled as median values

s significant, $p \leq 0.05$

ns non-significant, $p > 0.05$

[#] Median, d days, w weeks, m months, CGM continuous glucose measurement, CL closed loop, OL open loop, NR no restrictions, NS not specified, MPC model predictive control, PID-IFB proportional integral derivative insulin feedback, NI no information

[†] During the day, research staff accompanied the participant

^{†*} During the CL period, the initial 6 days were spent in a hotel

^a Insulin combined with the use of glucagon in CL modus

^b In adults, the OL period was performed in the outpatient setting, while the CL period was performed in an 8-km² area accompanied by study staff, with the night spent in a hotel, where blood samples were drawn every 30 min. In adolescents, the OL and CL periods were performed in a diabetes camp

Table 2 Results of the PubMed search for long-term studies (≥ 5 days) with eligible data published between 2014 and 2016 on continuous closed-loop versus open-loop control during the day

Study	Included (N)	HbA1c (%)	Evaluated (N)	Observation period		Physical activity during CL period	CL period	CGM	Algorithm	Defined glucose range (mmol/L)	Time in hypoglycemia (%)	Time in euglycemia (%)	Time in hyperglycemia (%)
				OL	CL								
Lecarathna [35]	21 adults	7.6	17	7 d	7 d	Advised not to drive or to undertake strenuous physical exercise under CL, but usual daily activities were allowed	83.0% of the total time (day and night)	FreeStyle Navigator; Abbott	Control to range MPC	[3.9, 10]	-	72.5 CL vs 65.4 OL (s) [#]	-
Thabit [30]	33 adults	8.5	32 CL, 33 OL	12 w	12 w	CL not used during physical activity during the initial 2 weeks	08.00–24.00	FreeStyle Navigator, Abbott	Control to range MPC	[3.9, 10]	3.0 CL vs 2.7 OL (ns)	62.9 CL vs 56.2 OL (s)	33.9 CL vs 39.7 OL (s)
De Bock [37]	8 adults/ adolescents	7.5	8	5 d	5 d	NR	NI	Enlite II, MiniLink REAL-time sensor, Medtronic	PID	[4.0, 9.9]	NI	66.7 CL vs 57.5 OL (ns) [#]	NI
Renard [31]	20 adults	8.2	20	1 m	1 m	NR	08.00–20.00	G4 Platinum, Dexcom	Control to target MPC	[3.9, 10]	2.3 CL vs 3.4 OL (s)	64.9 CL vs 60.7 OL (ns)	32.8 CL vs 35.8 OL (ns)

The studies had no restrictions regarding meals significant, $p \leq 0.05$

ns nonsignificant, $p > 0.05$

HbA1c values and values for the percentage of time that glucose was within the defined range are reported as mean values unless they are labeled as median values

[#] Median, *d* days, *w* weeks, *m* months, *CGM* continuous glucose measurement, *CL* closed loop, *OL* open loop, *NR* no restrictions, *NI* not specified, *MPC* model predictive control, *PID-IFB* proportional integral derivative insulin feedback, *NI* no information

range [29, 35]. Among the seven day-and-night closed-loop control studies included in Table 1, four found that more time was spent within the therapeutic range [29–31, 35], three found that less time was spent in hypoglycemia [29–31], and three found that less time was spent in hyperglycemia [29, 30, 35] than when open-loop control was employed. The longest day-and-night study with closed-loop control lasted 12 weeks [30].

At present, several studies with even longer periods of outpatient double SC closed-loop control are ongoing. While there are many studies which show that double subcutaneous closed-loop control is better at keeping blood glucose within the therapeutic range and is safer (considering the time spent in hypo- and hyperglycemia) than traditional open-loop control, improved average glucose levels are not a uniform finding when double subcutaneous closed-loop control is applied.

The Influence of Latency on Control System Performance

“Latency” and similar terms that are used in the AP literature relate to several dynamic phenomena that are of fundamental importance in a closed-loop control system such as an AP. We therefore offer a brief and pragmatic explanation of the most prominent concepts—namely time delays and time constants—to aid readers who are not familiar with dynamic systems theory [42]. The applicability of time constants in the present context is justified by the fact that the human glucose metabolic system is predominantly linear within its normal operating range and can thus be well approximated by linear models [43].

A time delay τ (cf. Fig. 1b) is typically associated with the transportation of a substance over a certain distance (e.g., the transport of glucose or insulin through the circulatory system or through tissue), and it denotes the time that passes from the application of a stimulus to a system until the first trace of the incident is theoretically detectable in the system’s output.

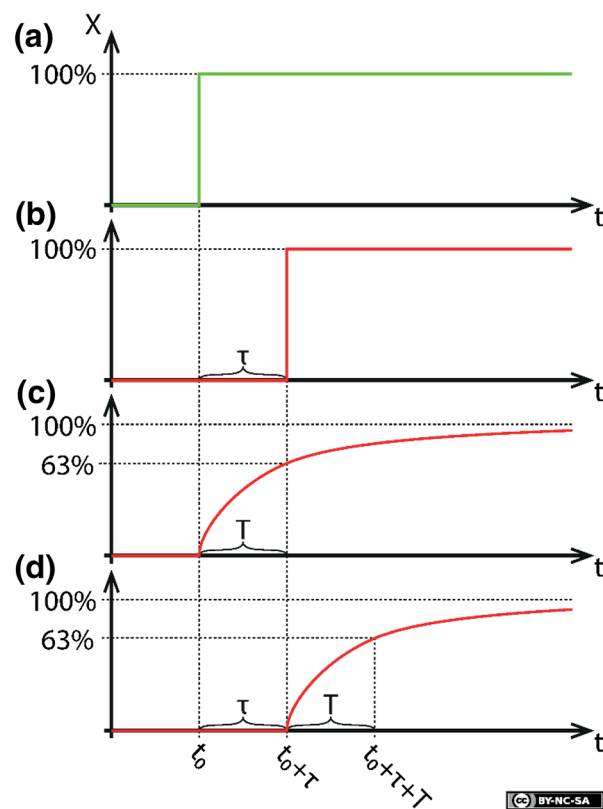


Fig. 1a–d Illustration of the concepts of a time delay (τ) and a time constant (T). The system stimulus is shown in **a**, while the other figures illustrate the output from a system that presents **b** a time delay, **c** a time constant, and **d** both. This figure is licensed for publication under a Creative Commons BY-NC-SA 4.0 license

A time constant T (Fig. 1c) is associated with, for example, the diffusion of a substance across a thin, semipermeable barrier separating two compartments, each of which has a uniform concentration of the substance (e.g., the diffusion of glucose or insulin across cell membranes, or across a protective membrane separating a glucose sensor from the surrounding fluid). A concentration gradient across the barrier will result in the net transport of the substance towards the region of lowest concentration, which gradually reduces the gradient until a dynamic equilibrium is reached. The time constant T associated with this process is the time from the initial establishment of the gradient until the concentration has reached 63% of its asymptotic level.

The effect of a time constant can in part be negated by appropriately filtering the output signal; this is limited only by the signal-to-noise ratio. In contrast, time delays cannot be negated in real time because this would require the ability to predict future events.

When it comes to closed-loop control, both time delays and time constants limit the obtainable bandwidth (i.e., the usable frequency range) of a closed-loop system. In an AP system exhibiting multiple time constants and/or delays (Fig. 1d) in the path from infused insulin to measured glucose, it is the sum of all the time delays and the larger time constant(s) that limit how quickly the AP can respond in order to correct glucose level deviations; larger latencies inevitably lead to larger glucose level fluctuations. This fact is at the core of this paper's message.

Insulin Physiology

In a healthy nondiabetic person, insulin is released from the β cells in the pancreas 2–3 min after the first increase in circulating glucose [44, 45]. This first phase of insulin response consists of the release of stored insulin and proinsulin from granules within the β cells. After about 10 min, a second and much stronger phase of insulin release commences. This phase consists of freshly synthesized insulin in response to the increased glucose levels sensed by the β cells, and lasts until the glucose levels normalize. At the end of this process, meal-initiated insulin secretion is shut off and insulin secretion is kept at a low level to maintain a steady glucose level. This biphasic pattern is only seen during fast changes in glucose levels as achieved by intravenous (IV) glucose infusions; it is absent during oral glucose loads, where only the second phase of insulin release is observed [45–47].

In the fasting state, insulin is typically released in bursts 4–5 min apart, and the half-life of insulin in the blood is about 11 min. During the fasting state, approximately 70–75% of the insulin is secreted in a pulsatory manner in a canine model [48, 49]. Between these bursts, there is little or no release of insulin

from the β cells. It is not known how this release of insulin from β cells is synchronized. However, this pulsatile pattern may be an important factor in the effect of insulin at the cellular level, as has been shown for other hormones with pulsatile release. The pulsatile delivery of insulin to the liver may also be important for increasing hepatic insulin sensitivity and achieving the full effect of insulin [48, 50, 51]. In healthy lean subjects without diabetes, approximately 50% of the insulin appearing in the peripheral circulation is delivered during the basal state in-between meals [52].

Insulin from the pancreatic β cells is released to the portal vein and arrives at the liver at a high concentration. During the passage through the liver, much of the insulin is absorbed in what is called the first-passage effect. Recent data indicate that as much as 80% of the insulin delivered in the bursts is absorbed, while as little as 20% is absorbed between bursts [53, 54]. This means that the exposure of the hepatocytes to insulin probably oscillates to a significantly greater degree than is reflected in the insulin-level oscillations in the portal and systemic circulation. The significance of this phenomenon is unknown. However, it may be important to the inhibition of hepatic glycogenolysis, the stimulation of glucose uptake from the blood arriving from the gastrointestinal tract, and the inhibition of hepatic gluconeogenesis. It has been suggested that the liver adapts its ability to withhold insulin to the levels in the portal circulation and the levels needed to suppress glucose in the systemic circulation [55–57].

After an oral glucose load or a normal meal in a healthy, lean, physically active person, both glucose and insulin will return to their starting levels within 120–150 min [58]. However, in overweight or obese subjects, it may take longer to return to the normal values [52]. In healthy subjects, this means that glucose and insulin will be at, or close to, their steady-state levels during shorter daytime periods and most of the night [52].

One of the important counterregulatory mechanisms to avoid hypoglycemia is the release of glucagon from pancreatic α cells. This mechanism is blunted in patients with

long-standing DM1, and although the α cells retain their ability to produce glucagon, the factors inducing the release of glucagon during hypoglycemia seem to be absent [59, 60].

Subcutaneous Continuous Glucose Monitoring

To our knowledge, all commercially available glucose monitoring systems measure glucose in SC tissue using enzymes belonging to the oxidoreductase family. The oxidation of glucose is followed by an electrochemical or optical assay procedure to derive the glucose concentration by measuring the enzymatic products using an amperometric or a chemoluminescent technique, depending on the assay [61, 62].

There is a physiologic latency from the point in time when a certain glucose level is present in the blood until the same level is reached in the interstitial fluid (ISF) in SC tissue [63–66] (Fig. 2). This latency is at least 6–7 min, but the physiologic latency between blood and ISF in SC tissue may be 15 min or more in some patients with DM1 [67–69]. Further, there is normally sensor latency, which is the latency between the appearance of glucose in the ISF surrounding the sensor and its consequent appearance in the sensor signal (Fig. 2). This sensor latency may consist of a reaction time (e.g., if glucose needs to react with enzymes or other substances in a typical amperometric sensor), a diffusion time (e.g., the time taken to

fill a probe volume in a spectroscopic sensor), or other sources of latency such as the computation time of the sensor's software. In addition, commercially available SC CGM devices do not perform truly continuous glucose measurements [70]. Most devices provide an average of the glucose level over the last 5 min once every 5 min. This averaging procedure is commonly used to reduce the effect of short-term random noise (which is due to both intrinsic properties of the sensor and extrinsic random factors originating from the sensor's chemical and physical environment) as well as to save battery capacity. Slowly varying signal variations due to, for example, biofouling are typically taken care of by repeatedly calibrating the sensor during its lifetime. Nevertheless, some recent CGM technology does not require frequent capillary calibrations [71].

The overall latency from physiologic and sensor-based sources may range from at least 8–10 min to above 20 min, which is far longer than the timescale required for real-time sensing of circulating glucose excursions experienced by healthy β cells. Some of these dynamics may be compensated for by the algorithm used to transform the raw sensor signal into an estimated glucose concentration. However, none of the companies in the CGM field publish their algorithms, so an external independent evaluation of the potential and limitations of this approach is not possible. The precision and accuracy of CGM have steadily

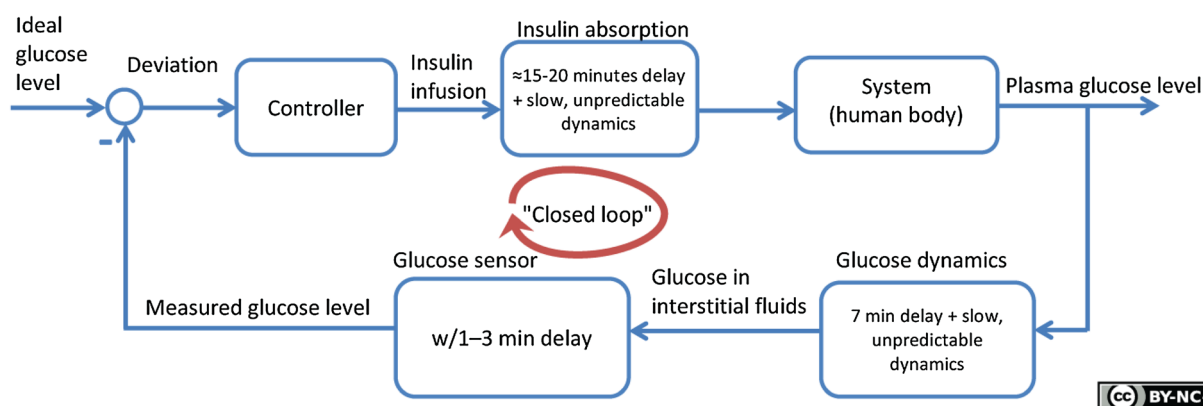


Fig. 2 Illustration of an artificial pancreas based on the double subcutaneous approach, including sources of delay. Reproduced with permission from [101]

improved, but such measurements still present limitations [72]. Although certain anthropometric measures (height, weight, skin thickness) seem to have little influence on accuracy, the impact of the foreign body response potentially limits the longevity of transcutaneous sensors [62, 70]. Further, although improved in the latest versions of CGM devices, the local ISF glucose level and thus the observed SC CGM sensor accuracy relative to blood glucose may be significantly influenced by local effects such as skin temperature, movements, the foreign body reaction, and pressure [73]. SC CGM devices typically show reduced accuracy for the first couple of days after insertion [62, 74]. This limitation should not be overlooked for a sensor with a usable lifetime of seven days. Certain drugs are also known to interfere with the measurements; for instance, the commonly used drug acetaminophen disturbs the enzyme-based CGM such that it leads to the overestimation of glucose levels in the ISF [75–77]. In addition, the mean average relative difference (MARD) between the measured and true glucose levels will be larger during periods of rapidly changing blood glucose than during periods of more slowly changing glucose levels [78]. An important safety issue is that current CGMs show their lowest concordance when capillary glucose is measured in the lower or hypoglycemic range. Although evaluations of the hypoglycemic range are often missing from reports evaluating CGM, there are examples which demonstrate that deviations from capillary measurements are highest when measurements are in the hypoglycemic range as compared to other ranges [79–82]. In other words, improvements to CGM are needed before it truly reflects blood glucose levels in a robust and reliable way.

One aspect of SC CGM that has hardly been discussed is the inflammatory reaction that is initiated whenever a foreign body is introduced into SC tissue [62, 83]. Patients experience this as a drift in sensor readings during the period in which they wear the sensor, and this partly explains why sensors need to be calibrated regularly. After decades of SC insulin infusion, most patients with DM1 have varying degrees of SC fibrous tissue formation at insulin injection

sites. The fibrous-tissue-initiating effect of decades of SC CGM use adds to the fibrous tissue formation induced by SC insulin infusion. Most patients that are using SC CGM have used it for less than a decade. Accordingly, one might expect less predictable SC insulin absorption in patients with DM1 when they have been using this new technology in combination with SC insulin infusion for decades.

One challenge when designing an AP is the need for redundancy in glucose sensing. Ideally, this should be achieved by sensing glucose via two completely different techniques in two different tissues. Some AP groups have introduced redundancy by using two identical CGMs concomitantly [22, 23, 26–28]. A downside of this is that it is a weak kind of redundancy and a probable cause of increasing long-term fibrous tissue formation.

Subcutaneous Insulin Delivery

State of the art insulin delivery in patients with DM1 is continuous injection from an insulin pump via a flexible plastic cannula inserted into subcutaneous tissue [84] (“CSII”). The insertion of a foreign body into subcutaneous tissue leads to a foreign body reaction. This effect can be reduced if the cannula is substituted and inserted at a different site after a few days. Local skin complaints (pain, lipohypertrophy) at insertion sites are quite common among insulin-treated patients, where lipohypertrophy is a consequence of the ability of insulin to stimulate local growth. A more important effect is that the pharmacokinetics of insulin uptake are probably altered in these patients, although the results of the few studies that address this issue are conflicting [85]. In the clinical setting, patients who have had DM1 for decades often report that their meal bolus expires earlier, or the opposite—that it has a delaying effect [86].

Importantly, fibrous tissue formation may cause varying and unpredictable absorption of insulin, and it is a major cause of insufficient blood glucose control and unpredictable hypoglycemic episodes. Varying insulin absorption can also occur independent of any foreign body reaction or fibrous tissue formation [86]. After a

single injection of the fastest-acting “meal” insulin, the maximum insulin concentration in the blood is reached after 45 min, and the insulin level in the blood is still markedly increased after 3 h [87]. More importantly, the glucose-lowering effect is at its maximum between 90 and 120 min after injection, and this effect is still present after more than 5 h.

Although rapid-acting insulin yields more stable results when delivered by CSII as compared to intermittent SC bolus deposits, considerable day-to-day variation is still observed [88]. This intra-individual effect may vary from hour to hour, and may depend on the local skin temperature (which affects subcutaneous blood flow and hence insulin absorption [89]). The same may be true of physical activity, as it results in increased SC blood flow (to get rid of heat) and induces motion due to the vigorous use of the underlying muscles. The accumulation of SC fibrous tissue after years or decades of insulin injections may markedly increase insulin absorption variability. There is also interindividual variation, which may increase the need for individually adjusted algorithms in APs.

When using CSII, there is also the challenge of transporting the insulin from the ampulla in the device to the SC injection site. This is prone to several errors, which could be down to the user or due to equipment failure [90].

Physical Activity

As with all patients, physical activity increases insulin sensitivity in patients with DM1 [91]. This is frequently observed in DM1 patients who regularly exercise in the evening. Hypoglycemic episodes often occur in such patients later in the evening or during the night. However, “unexplained” hypoglycemic episodes are also often experienced the next morning or later the next day. This may even happen in cases where the patient has increased food intake and/or reduced insulin doses due to the exercise.

There is no official recommendation regarding the amount or type of carbohydrate patients with DM1 should ingest to avoid hypoglycemia

during exercise. A clamp study found IV glucose demand changed as the level of physical exercise was increased consecutively. The glucose infusion rate was increased at a moderately intense level of exercise, while the need for IV glucose disappeared during high-intensity exercise [92]. The latter illustrates the complexity involved in attempting to take physical activity into account, as the need for insulin can vary during exercise in ways that are difficult to predict.

It was recently reported that the effects of physical exercise on blood glucose depend on the nature of the physical exercise; i.e., its duration, degree of vigorousness, and the type of physical exercise performed [93]. It seems that the glucose level initially drops more quickly during aerobic activity than resistance activity, but resistance activity leads to a longer-lasting lowering of the glucose after the activity is finished [94]. Research groups who have accounted for physical activity in their algorithms have achieved lower hypoglycemic episode rates during physical activity, but long-term studies are needed to check that these lowered rates do not come at the cost of more time spent in hyperglycemia [95–97].

Any AP with a feedback controller exclusively based on blood glucose levels would need to accept markedly less satisfactory glucose control in order to avoid both short- and medium-term hypoglycemic episodes due to physical activity. In particular, this problem would become more pressing if unpredicted major exercise was to be performed within the first few hours after a meal, as fast-acting “meal” insulin lowers glucose even 5 h after administration. Due to the relatively long half-life of SC-delivered insulin, this issue is difficult to resolve unless a compensating factor such as glucagon is applied [22, 29, 98].

Meals

Most studies of AP have used meal announcement, which involves the patient either deciding the amount of insulin given with a meal or estimating the amount of carbohydrates and leaving it to the algorithm of the AP to suggest

the insulin to be given with the meal [21, 23–35]. Meal-related insulin administration is a major challenge for both an AP and patients with DM1.

Only two smaller studies by a Dutch group have tested a bihormonal (insulin and glucagon) AP without meal announcements and user-dependent insulin determination [22, 98]. In the first study, an AP was used for only two days in a limited number of highly surveyed patients [22]. Interestingly, mean glucose levels did not improve compared to the those obtained with the usual open-loop treatment, while night-time glucose levels improved.

In healthy nondiabetic individuals, the first phase of insulin release (see the “[Insulin Physiology](#)” section) is probably important for restricting the total meal-induced increase in glucose. The larger release of insulin seen after about 10 min (the second phase) is essential for handling the increase in glucose within a couple of hours. Thus, it is essential for an AP to be able to identify a meal as soon as possible after the meal has been initiated if it is to deliver insulin early enough to achieve proper control of meal-induced glucose excursions. The time until automated meal detection is significantly influenced by the latency of the SC CGM if the detection algorithm is based on these commonly available measurements.

Measures Implemented to Overcome Safety Issues

Several studies of double SC AP have used two SC glucose sensors, where the second sensor signal is not actively used until the first sensor fails [23, 26–28]. One study did apply a rule where an alarm was triggered if the difference between the two sensors exceeded >20% when the glucose level was lower than 8 mmol/L, or if the difference between the sensors exceeded >1.5 mmol/L when the glucose level was above 8 mmol/L [22].

Some control methods follow certain safety rules; for instance, only a partial (pre-meal) bolus is given at the start of the meal in order to avoid postprandial hypoglycemia, and an extra post-meal bolus is delivered if hyperglycemia

becomes imminent [26, 28]. Other efforts to avoid hypoglycemia allow the algorithm to adapt its insulin sensitivity factor based on the rate of change in postprandial glucose excursions, and/or to use a “withhold action threshold” by defining an upper limit for the rate of change in insulin delivery as compared to baseline insulin delivery [22, 28]. Some control methods also try to achieve safe insulin delivery at decreasing glucose values by, for instance, implementing a time-limited suspend at a defined hypoglycemic limit when hypoglycemia is present or imminent, and/or by simply alerting the user to the need to ingest carbohydrates at low glucose values [25, 26]. Some groups apply glucagon, typically by giving increasing pulses of glucagon at certain glucose “action thresholds” defined by glucose levels or defined changes in the rate of decrease in glucose [22, 29]. Other control methods also account for the potential “stacking” of previously delivered insulin [25–27, 29].

DISCUSSION

Most of the studies published in this field have used an AP based on the double SC approach, and most of those studies were designed to evaluate performance during the night; there have been relatively few day-time studies (although some of the night-time studies included a short post-breakfast period) [21, 23–41]. Long-term studies (≥ 5 days) show that time in the euglycemic state (defined as glucose levels between 3.9 and 8–10 mmol/L) is increased when double SC AP is applied rather than a control period with sensor-augmented pumps (SAP) (Tables 1, 2 and 3). Some (but not all) studies show that time spent in hypoglycemia is decreased by the use of double SC AP. In addition, most studies show a significant reduction in the time spent in hyperglycemia during the use of double SC AP, but the time spent in hyperglycemia was still around 20–30% in most of the long-term studies shown in Tables 1 and 2. Interestingly, when an extended long-term study compared the benefit of one month of 24-h double SC CL with the results obtained in a previous trial (six weeks of nightly

Table 3 Advantages of the double subcutaneous approach

Anticipation of changes in insulin demand during the day and night (in contrast to sensor-augmented CSII)
More time spent in the therapeutic range (i.e., less time spent in the hypoglycemic and hyperglycemic ranges) as compared to sensor-augmented CSII
Easily managed by the user on a daily basis
Based on available off the shelf technology

Table 4 Limitations of an artificial pancreas based on the double subcutaneous approach

Low accuracy of glucose measurements, especially at lower glucose levels
User-dependent calibrations of continuous glucose measurement
Delayed insulin absorption (results in a delay in the onset of the effect of insulin when demanded)
Unpredictable variations in subcutaneous insulin absorption
Ongoing effect ("tail") of previously delivered insulin when glucose approaches hypoglycemic levels
Still requires user input regarding meal bolus delivery and estimation of carbohydrate and fat contents of meals
Varying improvement in average glucose levels

CL versus SAP), no additional benefit of 24-h CL as compared to night-time double SC CL was found [31].

An approach utilizing glucagon to counteract the progression of glucose lowering towards hypoglycemia achieved a notable increase in euglycemia time during day and night, but this approach required increased consumption of insulin [29].

There are two major limitations of the double SC approach that hamper progression towards the ideal AP (Table 4 and 5). First, there are the latencies associated with SC CGM based on presently available technology. The combined physiological and sensor-based latency is at least 10 min, but may be more in some patients. Combined with the fact that the accuracy and robustness of CGM are still not optimal, this means that it takes time for the AP to identify a meal-induced increase in glucose levels and initiate a meal dose of insulin. In any case, this will be too late to mimic both the first phase and the early part of the second phase of the physiological meal-induced insulin increase seen in healthy nondiabetic people. Perhaps

equally important is the fact that it takes even more time to supply the liver with blood saturated with the quantity of insulin tailored to stimulate glucose uptake and suppress gluconeogenesis.

Secondly, and probably more importantly, the slow absorption of insulin from SC tissue and the substantially delayed glucose-lowering effect is still present 5 h after the SC delivery of insulin. This means that any insulin dose that will regularly normalize glucose levels within a couple of hours after a meal (to the same degree as in healthy people) will induce serious late postprandial hypoglycemia if the patient does not ingest more food in the postprandial period. In fact, the need for many patients with DM1 to eat between meals to avoid hypoglycemia probably contributes to the increased body weight of DM1 patients compared to the non-diabetic population [99].

Mealtime excursions remain a challenge during the use of double SC AP. To our knowledge, only one study has been able to maintain daytime glucose control with the aid of double SC AP without including announcements of

Table 5 Possible ways to improve the double subcutaneous approach

Use faster and more accurate ways of measuring glucose
Employ several identical sensors or a mixture of several different sensor technologies (“sensor fusion”)
Use sensors that require less frequent calibration
Use sensors with longer durations/lifespans
Employ faster-acting insulins
Provide meal detection tools
Tools for detecting physical activity

meals and physical activity [22]. That study, however, had several weaknesses, as it was small-sized, of short duration, suffered from technical problems in 30% of the participants, and had a rather high glucose threshold of 6.5 mmol/L before insulin delivery was started [22]. Such a high threshold for glucose delivery can act as a safety buffer to avoid hypoglycemia, compensating for the slow pharmacokinetics of SC-delivered insulin and the latency of glucose feedback, but it also implies that more time is spent in the hyperglycemic range.

These physiologic realities are reflected in the fact that most studies of AP report improved night-time glucose control (i.e., improvement in the near-fasting and fasting state). Data from daytime studies are often reported not as daytime-only data but in combined day-and-night datasets, which makes it difficult for the reader to distinguish the daytime effect from the night-time effect [29, 36, 39]. Time in hyperglycemia during the daytime in the few studies which explicitly report daytime data appears to be higher than the time in hyperglycemia reported for 24-h data (Table 2) [30, 31].

Lastly, but importantly, there is another challenge associated with the use of new invasive technologies such as the double SC approach which require user maintenance: user fatigue, which can increase with the number of systems (e.g., sensors) that must be maintained [100].

CONCLUSIONS

A fully automated robust AP that normalizes or near-normalizes glucose levels in patients with DM1 without risking serious hypoglycemia is difficult to achieve using the double SC approach (i.e., by measuring glucose and delivering insulin into subcutaneous tissue). The major obstacle is the slow and sometimes unpredictable absorption and thus the delayed glucose-lowering effect of SC-delivered insulin. However, SC glucose sensing also has an inherent and probably unavoidable physiologic latency, adding to the delay in SC insulin absorption.

The major challenge is that the present off-the-shelf technology used for the double SC approach cannot handle meal-induced glucose excursions without incurring a substantial risk of serious late postprandial hypoglycemia. Accordingly, patients, healthcare professionals, and insurance companies should not be given the impression that a robust AP that can normalize or near-normalize glucose levels by applying the double SC approach is within reach using current technology.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

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