Advances in pump technology: insulin patch pumps, combined pumps and glucose sensors, and implanted pumps

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Abstract

This review discusses the most recent developments in insulin pump technology. The benefits of the insulin pump to patients with type 1 diabetes are recognized both for its metabolic effectiveness and its positive effects on quality of life. The current pumps are reliable, small and light, and are becoming more and more sophisticated. Nevertheless, there remain practical and psychological constraints for the patient. However, recent patch-pump advances should simplify the technical aspects of pump treatment and enhance patient comfort. Another advance combines the insulin pump with a glucose sensor. Such a combination is logical for optimizing pump use and, to that end, developing an automated or ‘closed-loop’ system that permits the delivery of subcutaneous insulin adjusted according to measured levels of subcutaneous glucose. Finally, implanted insulin pumps have proven their worth not only because of their simple use, but also for their contribution in the artificial pancreas project. Indeed, the prompt response with intraperitoneal administration of insulin makes it of interest for use in a closed-loop system.

Keywords: Insulin patch pump; Coupled sensor pump; Implanted insulin pump; Review

Résumé

Regard prospectif sur la technologie des pompes à insuline : pompes-patch, pompes couplées aux capteurs de glucose, pompes implantées

Cette revue présente les développements récents et en perspective de la technologie des pompes à insuline. Les avantages de la pompe à insuline chez les patients diabétiques de type 1 sont reconnus que ce soit pour son efficacité métabolique ou pour son bénéfice sur la qualité de vie. Les pompes actuelles sont fiables, petites et légères et de plus en plus sophistiquées. Il persiste néanmoins pour le patient des contraintes pratiques et psychologiques. Les avancées récentes visent à développer des pompes patch qui devraient simplifier l’aspect technique du traitement et améliorer le confort des patients. Une autre avancée concerne le couple pompe à insuline-capteur de glucose, combinaison logique pour optimiser l’utilisation de la pompe avec en perspective l’élaboration d’un système automatisé ou « boucle fermée » permettant une délivrance d’insuline sous-cutanée ajustée à la mesure sous-cutanée du glucose. Enfin les pompes à insuline implantées ont fait leurs preuves dans leur utilisation simple mais aussi dans un projet de pancréas artificiel. En effet, l’administration intrapéritonéale de l’insuline a une grande réactivité, intéressante pour son utilisation dans un système de boucle fermée.

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Mots clés : Pompe-patch ; Pompe couplée à un capteur de glucose ; Pompe implantée ; Revue générale

1. Introduction

In patients with type 1 diabetes, the benefits to glycaemic control and quality of life of external insulin pumps have been clearly established [1]. The main indications for an external pump include persistently elevated HbA1c, despite intensive multiple-injection insulin therapy, repeated hypoglycaemia and significant glycaemic variability [2]. Other medical circumstances may also warrant pump treatment, such as pregnancy and type 2 diabetes that has failed to respond to intensified multiple-injection insulin therapy. Specific paediatric indications may also be seen in certain cases [2].

Today’s insulin pumps are the result of decades of design and engineering efforts towards the development of reliable, secure and user-friendly modern pumps. These pumps are small and light, and offer technical solutions that are suited to diabetic patients’ needs. Their integrated software has also evolved, and can now keep track of the delivered insulin and blood glucose measurements, enable bolus calculation and permit link-ups with other compatible systems.

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The most recent pump-technology research concerns the development of insulin patch pumps and pumps coupled with glucose sensors. The present review examines their basic concepts and describes only those devices already available or under development, and reports, if need be, the results of clinical studies. The technology of the implanted insulin pump is included in this review as well.

2. Insulin patch pumps

Although the benefits of external pump treatment have been clearly established, the treatment modality nonetheless requires strong patient motivation and involvement. However, certain features of the external pump could be improved to reduce treatment constraints and improve patients’ quality of life. Indeed, the initial technical education on how to use the pump and insert the catheter takes time, some patients have the impression of being attached to an external object; equipment problems, such as catheter occlusion and bent cannulae, are common occurrences, disconnecting the pump is recommended before taking a shower, or engaging in water or other sports activities.

Recent technological progress has resulted in the development of “insulin patch pumps” that ought to simplify the technical aspects of treatment and improve patient comfort [3,4]. The term “patch”, however, may be a misnomer. Although these new pumps are smaller and free of tubes, they often have subcutaneous cannulae through which insulin is injected. The patch pump is nevertheless an innovative system in the field of insulin pumps. The concept comprises an insulin reservoir, delivery system and cannula, all of which are integrated into a small, wearable, disposable or semi-disposable device. The patch pump combines the functions of a conventional insulin pump with the following advantages: by eliminating the tubing, it is easy to use; to initiate pumping requires only simplified training; and it is discreet.

The development of the patch pump has been initiated by a large number of companies ranging from start-ups to established firms. At present, a few of these pumps have been approved for marketing in the US by the Food and Drug Administration (FDA), while a wide range of other devices is also reported to be currently under development [5].

2.1. Currently available insulin patch pumps

Only the OmniPod® (Insulet Corp., Bedford, MA, USA) (Fig. 1) is currently available for use, and has been sold in the US for several years [5]. The device, distributed by Ypsomed, will soon be available in France. The pump/reservoir unit (Pod) is a tube-free disposable device applied to the body with adhesive, and changed every 3 days. The Pod has an integrated infusion set and automated inserter, and communicates wirelessly with the personal data manager (PDM), a separate controller device that manages insulin delivery. In addition, the PDM contains an integrated blood glucose meter and food database, and is waterproof, allowing it to be worn during showering or swimming. In one short-term study [6], type 1 diabetic patients preferred using the Pod to their conventional pump. Another prospective study [7] demonstrated the safety and efficacy of 500 U of insulin delivered by OmniPod in type 2 diabetes insulin-resistant patients.

2.2. Approved insulin patch pumps not yet available

Two patch pumps have been approved by the FDA, but are not yet on the market [5]. The Solo™ MicroPump Insulin Delivery System (Medingo US Inc., Tampa, FL, USA) (Fig. 2) has two parts: the micropump itself; and a remote device that programmes and directs the micropump. The micropump is small and slim, and consists of a 2 mL insulin reservoir, a cannula cradle infusion set and a pump base. The disposable insulin reservoir and cannula must be replaced every 2 to 3 days. The pump base includes a reusable 90-day unit that holds the electronics, memory, pump motor and bolus buttons. The base must be clicked out of the cradle before swimming or engaging in contact sports. Boluses are delivered via the remote device or directly from the pump.

The Finesse™ patch pen (Caliba Medical, Inc., Redwood City, CA, USA) is a disposable and completely manual system that only delivers insulin boluses. As there are no electronics, the bolus is delivered by depressing bolus-release buttons.

2.3. Insulin patch pumps under development

There are numerous patch pumps currently being developed [5]. The Cellnovo™ pump (Cellnovo Ltd, London, United Kingdom) is a minipump that is programmable via a mobile handset based on the principles of Apple technology; it consists of a controller for the insulin pump and a blood glucose meter, and also contains a food library. The handset transmits data to a centralized server. The minipump’s insulin reservoir has a capacity of either 0.5 ml or 1.5 ml, and is connected to a cannula and minitubing, each of which needs to be replaced every 3 days. The pump battery is rechargeable.
The V-Go™ pump (Valeritas, Inc., Bridgewater, NJ, USA) is a fully disposable transdermal device with a preset basal rate and on-demand bolus delivery. The device needs to be replaced daily. It has no programming, no electronics and no batteries.

The JewelPUMP™ (Debiotech SA, Lausanne and STMicroelectronics, Geneva, Switzerland) is based on the MEMS Nanopump™ technology and comprises two parts: the reusable part contains the electronics and includes remote communication for distant programming; the other, disposable part includes a reservoir, pumping mechanism and batteries. The insulin reservoir is refilled every 6 days.

The CeQu™ pump (Montreux, Switzerland) is intended for type 2 diabetes patients. The pump delivers a constant basal rate and on-demand bolus delivery at the push of a button.

The PassPort™ Transdermal System (Altea Therapeutics Corp., Atlanta, GA, USA), currently under phase-I clinical evaluation, dispenses only a basal rate of insulin. The system includes an applicator and a PassPort™ Patch, which contains a reservoir and a tiny metallic filament screen known as the “porator”. The applicator delivers an electrical charge to the porator, thereby galvanizing the filaments and scattering the closest skin cells. Micropores are thus created on the surface of the skin, permitting transdermal passage of insulin. The delivery method can be configured to achieve either systemic or localized action of the therapeutic agent. The aqueous micropores allow the rapid and sustained flow not only of insulin, but also of proteins, peptides, carbohydrates and small molecules into the body without the use of needles or pumps.

The NiliPatch Disposable Insulin Pump System (NiliMEDIX Ltd, Tirat-Carmel, Israel) delivers basal and bolus insulin. The pump uses a pressure-triggered release mechanism, and is controlled by a system of valves and sensors. The NiliPatch pump has been certified for marketing in the European Union and Israel.

The Freehand™ system (Medsolve Technologies, Inc., Manhattan Beach, CA, USA) is a remote-controlled basal and bolus insulin-delivery pump system with a 3-month lifetime. The system offers seven basal profiles. Basal delivery can be temporarily suspended, and boluses can be delivered either remotely or manually.

Little information is available at this time on the following models supposedly under development: the Medipacs patch pump (Medipacs, Inc., San Diego, CA, USA); the Medtronic patch delivery system (Medtronic, Inc., Minneapolis, MN, USA) and the SteadyMed patch pump (SteadyMed Ltd, Tel-Aviv, Israel).

In summary, there are many patch pumps at various stages of development, but few are currently on the market or anticipated to soon be on the market. The very concept of a patch pump will improve patient comfort and eventually improve patient compliance with treatment. Moreover, it should reduce barriers to pump acceptance, particularly in type 2 diabetic patients.

3. Insulin pumps coupled with glucose sensors

The combined use of real-time continuous glucose monitoring (RT-CGM) and continuous subcutaneous insulin infusion (CSII) via an external pump is a logical development with a view towards an artificial pancreas for the optimal treatment of type 1 diabetes. The goal is to implement an automated system or “closed loop” that permits the delivery of subcutaneous insulin adjusted to measured levels of subcutaneous glucose.

3.1. Non-automated coupling of insulin pumps and glucose sensors

While awaiting the development of an artificial pancreas, a preliminary step is the non-automated coupling of an insulin pump to a glucose sensor. The combined use of both systems appears consistent with the conceptual plan to optimize use of the pump. The patient can continuously adjust the delivery of insulin based on the values and trends indicated by real-time data from the glucose sensor. This is an example of an “open-loop” device: the patient can maintain glucose control by interpreting the data from RT-CGM, and use it to modulate insulin basal rate, temporarily stop the pump and/or deliver additional insulin boluses. The theoretical value is such
that systems incorporating insulin pumps and glucose sensors are already available to patients. These sensor-augmented pump devices include a subcutaneous glucose sensor with a 6 to 7 day lifetime that communicates via telemetry with an external insulin pump. The pump’s screen displays glucose sensor data and emits an audible alarm whenever high or low values are detected. The first such system, sold in 2006, was the MiniMed Paradigm REAL-Time System® (Medtronic, Inc.). Another system soon to appear on the market is the Animas® Vibe™ (Animas Corp., West Chester, PA, USA).

Self-monitoring of blood glucose (SMBG), in its common clinical use, only reports glycaemia levels at a precise point in time, generally before meals and at bedtime. It has been shown that the frequency of SMBG is inversely correlated to the value of HbA1c [8]. In practice, most patients rarely take more than four to six blood glucose measurements per day. On the other hand, even if sustained, the SMBG provides glucose information for only one point in time, with no information on the kinetics of blood glucose and/or its rate of change. For these reasons, RT-CGM from the start appears to have added value when combined with CSII [9]. This added value can be examined in recent randomized studies evaluating the effectiveness of sensor-augmented pumps.

3.1.1. Effectiveness of RT-CGM associated with an insulin pump

All of the studies [10-13], with the exception of the first [10], confirmed the efficacy of RT-CGM associated with an insulin pump in reducing HbA1c, even though the benefit was sometimes observed only in subgroups of patients. The first study [10] involved poorly controlled type 1 diabetic patients already being treated with an insulin pump. These patients were randomized into two groups: the first continued with SMBG and pump therapy; while the second was treated with a sensor-augmented pump (the MiniMed Paradigm REAL-Time System). After 6 months, the HbA1c decrease of about 0.6% to 0.7% was similar in both groups. Although the overall results were negative in terms of added value with RT-CGM, post-hoc analysis highlighted the importance of how long the glucose sensor was worn. Of the patients using the sensor >60% of the time, there was an HbA1c decrease of almost 0.9% during the study. In contrast, the control of diabetes worsened in patients wearing the sensor < 60% of the time, with an HbA1c increase of almost 0.2%.

The French multicentre REAL Trend study [11] took into account this observation of the essential role of compliance with wearing the sensor. The study enrolled poorly controlled type 1 diabetes patients, treated with multiple daily insulin injections (MDI), who were randomized into two groups: the first group began therapy with a pump and conventional SMBG; the second group used a sensor-augmented pump (MiniMed Paradigm REAL-Time System). From the outset, the latter patients were asked to use the glucose sensor >70% of the time. After 6 months, the per-protocol analysis (patients compliant with sensor use) showed that HbA1c values were significantly different between the pump vs sensor-augmented pump groups (-0.55% vs -0.96%, respectively; P<0.005). The study further highlighted the need for a preparatory period of a few days for patients using the glucose sensor. This period enabled the patient to determine whether or not wearing the glucose sensor was tolerable in the medium term.

Unlike the two previous studies in the series, the STAR-3 study [12] lasted 1 year and not only evaluated RT-CGM, but the system combined with a sensor-augmented pump. STAR-3 involved poorly controlled type 1 diabetes patients treated with MDI and randomized into two groups: the first continued MDI treatment with SMBG; the second received sensor-augmented pump treatment (MiniMed Paradigm REAL-Time System). After 3 months and up to the end of the study, HbA1c was significantly improved in the sensor-augmented pump group compared with the MDI group (at 12 months, -0.8% vs -0.2%, respectively; P<0.001). In addition, the proportion of patients achieving the HbA1c target of <7% was almost three times higher in the sensor-augmented group. Again, compliance with sensor use was crucial for determining metabolic benefits: sensor frequency of use of 61–80% was associated with a reduction in HbA1c of 0.79%, while a use frequency of 81-100% was associated with a reduction of 1.21%. On analyzing the factors predictive of sensor-augmented pump’s metabolic benefit [13], the baseline predictors for HbA1c reduction were HbA1c level ≥9%, patient’s age ≥36 years at randomization and age at the onset of diabetes >17 years.

Thus, the REAL Trend and STAR-3 studies [11,12] clearly demonstrated the metabolic effectiveness of pump therapy optimized by glucose sensors, and the efficacy may even have been underestimated. The first reason is that the improvement in HbA1c was also observed in the control groups. These improvements may have been linked to intensification of SMBG as well as tight coaching by study investigators. Another reason is that the investigators themselves in the first study may not perhaps have had enough experience with RT-CGM.

The results of the SWITCH study [14], a multicentre randomized, controlled, crossover study, have not yet been reported, but the findings should resolve the question of added value with RT-CGM associated with CSII. Indeed, the study was designed to assess whether CGM provides any additional benefits to patients already being treated with a pump. It was carried out over two experimental periods of 6 months each, separated by a washout period of 4 months. The patients’ usual pump was replaced by a pump coupled with a glucose sensor. Patients were then randomized into one of two study arms. In one arm during the first 6 month period, the sensor was set to ON while, in the other arm, the sensor was set to OFF. The settings were then reversed for the second 6 month period.

3.1.2. Pump patients in other studies showing benefits with RT-CGM

The benefits of RT-CGM have been shown in other studies where the mode of insulin therapy was not modified at randomization, and where randomized patients in the glucose-sensor group
followed their previous insulin treatment [15,16]. One multicentre study sponsored by the Juvenile Diabetes Research Foundation (JDRF) [15] included type 1 diabetic patients receiving intensified insulin therapy, two-thirds of which were CSII. This study demonstrated that RT-CGM is effective for reducing HbA1c in patients aged >25 years, but has less effect in younger patients. Yet again, glycaemic control was improved with prolonged and sustained use of the sensor during the 6-month study. There was no difference in efficacy between patients using the pump and those receiving multiple injections of insulin.

More recently, a 1 year multicentre study was conducted by the EVADIAC sensor study group involving poorly controlled type 1 diabetic patients treated with a pump or multiple injections in the same proportions. Patients were randomized into three groups: a control group following the traditional SMBG; and two groups using RT-CGM, one ad libitum and the other with a frequency determined by the physician based on metabolic criteria. At 3 months, HbA1c improved significantly in both groups using the RT-CGM compared with the control group and at 1 year, the difference was 0.5%. Several factors were involved in this outcome, including adherence to sensor use, modality of insulin therapy and patients’ education. At 1 year, there was a significant HbA1c reduction of 0.67% in pump patients in the RT-CGM groups vs the control group. In patients using injections, HbA1c decreased by only 0.28%. This study also highlighted the impact of specific patients’ education that enabled them to properly interpret and use the CGM data. In contrast, a 6-month prospective study [17] concluded that CGM provided comparable benefits to metabolic control for patients using either MDI or CSII therapy.

In all these studies but one [10], the HbA1c reduction was not associated with an increase in severe or moderate hypoglycaemia. However, these trials were not designed to study hypoglycaemia, and the patients had not been selected on that basis. On the other hand, a randomized and controlled multicentre trial [18] was specifically designed to evaluate the effect of CGM on hypoglycaemia in type 1 diabetic patients who were well controlled (HbA1c<7.5%) and treated with either an insulin pump or multiple injections. The results of this 6-month study showed significantly reduced time spent in hypoglycaemia in patients who used CGM compared with SMBG, with a concomitant decrease in HbA1c.

In practice, hypoglycaemia is a major limiting factor for good glycaemic control, making the prevention of hypoglycaemia one of the most important benefits anticipated from glucose-sensor pumps.

### 3.1.3. Automated coupling of insulin pumps and glucose sensors for preventing hypoglycaemia

Hypoglycaemia alerts are integrated into RT-CGM systems. However, the DirectNet Study Group [19] showed that 71% of cases – specifically, children and adolescent patients – did not react to the hypoglycaemia alerts that occurred during sleep. This is important as most episodes of severe hypoglycaemia happen at night [20].

### 3.1.4. Suspending insulin delivery when hypoglycaemia is predicted

The idea is to use the coupled sensor-pump as a “partially closed loop” to defer the delivery of insulin when hypoglycaemia is predicted. Pilot-study results are encouraging [21-23]. These studies tested the functionality of an algorithm that detects pending hypoglycaemia, and assessed whether hypoglycaemia was prevented by temporary stoppage of the pump. The first study [21] involved 22 type 1 diabetic patients, treated with an insulin pump, who were asked to undergo RT-CGM twice with the FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA, USA). First, the basal rate of the insulin pump was gradually increased so as to induce hypoglycaemia (<60 mg/dL). Based on the insulin sensitivity noted in this experiment, the basal rate was increased again in a second test to induce a comparable fall in glucose and projected blood glucose of < 60 mg/dL. Data from the FreeStyle Navigator were reported in a database with two algorithms for predicting hypoglycaemia. From these models, the probability of hypoglycaemia was generated to produce an alarm. For each subject, only one of the two algorithms was used in the second test. When the algorithm predicted a future blood glucose of < 80 mg/dL, the insulin pump was stopped for a period of 90 min. With a 30 min prediction, 60% of hypoglycaemias were foreseen and prevented. With a 45 min prediction, 80% of hypoglycaemias were prevented. Hyperglycaemic rebound was not observed after temporarily stopping the pump.

In another study specifically addressing prevention of nocturnal hypoglycaemia [22], the hypoglycaemia-predicting algorithm (HPA) combined five separate algorithms, all based on CGM 1-min data. This HPA algorithm was developed from 21 studies using the FreeStyle Navigator system. The five pump-suspension algorithms were based on a 35 min prediction and used an 80 mg/dL glucose threshold. When two algorithms were used, hypoglycaemia was prevented in 75% of nights and in 84% of cases.

Yet another study [23] assessed the aggressiveness and effectiveness of HPA according to the settings for the following parameters: hypoglycaemia prediction time (35, 45 and 55 min); hypoglycaemia threshold value (70, 80 and 90 mg/dL); and the number of algorithms used (three, four and five). If, with a glucose threshold of 80 mg/dL, three of the five algorithms were used, then 91% of hypoglycaemias were predicted 35 min beforehand. If four algorithms were used, 82% of events were predicted 35-55 min ahead of time. According to individual sensitivities, these settings can differ from day to night, and modulate specificity and reduce the number of false alarms. However, as these clinical studies were conducted at a clinical research centre, real-life studies are now needed.

### 3.1.5. Suspending insulin delivery when hypoglycaemia is detected

A recent evolution [24] of the Paradigm REAL-Time pump is the Veo™ model (Medtronic), which has been available in
Europe for nearly 2 years. This system uses data transmitted by the glucose sensor to automatically suspend the delivery of insulin in cases of hypoglycaemia. This “automatic stop” (“low-glucose suspend”, or LGS, function) is interesting, but is activated only when the sensor detects interstitial glucose levels below a predetermined threshold rather than before the hypoglycaemia occurs. Clinical experience with the Paradigm Veo pump is still limited, and the efficacy of the system in reducing hypoglycaemia has only been evaluated in a few recent short-term studies [25,26]. One study was conducted in type 1 diabetic adults fitted with the Veo pump [25]. Hypoglycaemia events were examined during two consecutive periods. During the initial 2-week period, the automatic stop was not activated (LGS was set on OFF). Following this, during a second period of 3 weeks, the LGS was enabled (set on ON). The results showed that, in patients at high risk of hypoglycaemia, the LGS function significantly reduced nighttime hypoglycaemia duration with no hyperglycaemic rebound or ketosis. Similar results were reported in another study conducted in diabetic children and adolescents [26].

Major progress is expected in the field of glucose-sensing and insulin-delivery technology. As an example, systems could be designed to maintain glucose within the range of normoglycaemia. There would have to be an automatic stop of insulin infusion if glucose falls below a given threshold, and delivery of an insulin bolus if glucose rises above an upper threshold [27].

In summary, in its current application, the coupling of an insulin pump with a glucose sensor is an open-loop system in which the patient has to interpret data from RT-CGM to adapt the delivery of insulin. Unquestionably, studies have shown that combining RT-CGM and CSII rapidly improves glycemic control in a sustainable manner in type 1 diabetes patients. However, the device works best for motivated patients who are trained in intensive insulin therapy as well as in the interpretation of large amounts of complex CGM data. Nevertheless, the most recent technological progress used in actual clinical practice represents an early version of an artificial pancreas system also known as an “LGS system”.

4. Implanted pumps

The use of implanted insulin pumps began enthusiastically a little over 20 years ago. The objective was to free the patient from the constraints of injections as well as to develop the components for an implantable artificial pancreas by taking advantage of the benefits derived from the use of intraperitoneal insulin delivery.

4.1. The intraperitoneal route

Subcutaneous (SC) insulin absorption is slow, variable and induces secondary hyperinsulinaemia. These limitations have led to alternative routes being sought for continuous ambulatory infusion of insulin [28]. Studies in animals have shown the benefits of the intraperitoneal (IP) route, which has pharmacokinetics that are closer to physiological than the SC route [29].

After delivery into the peritoneal cavity, insulin is primarily resorbed in the portal vein. There is an approximately 50% degradation during the first hepatic passage, thereby recreating a physiological insulin gradient between the portal vein and systemic circulation [30]. Compared with the SC route, the IP route induces lower peripheral insulinemia while allowing resorption and a faster return to baseline plasma levels [31,32]. These insulin kinetics are more physiological [32], maintaining reproducibility of insulin profiles in the long term [33] and resulting in an improved glucagon response to hypoglycaemia [34].

The use of the IP route for type 1 diabetes treatment was made possible by the development of programmable implantable pumps that deliver insulin through an IP catheter. Pilot trials [35-37], conducted in the 1980s, demonstrated the feasibility, efficacy and safety of this therapeutic approach. Insulin therapy via an implanted pump began in 1989 with its primary development in France. As a result, the French data are foremost in the world. There are 15 centres in France included in the association EVADIAC (Evaluation dans le diabète du traitement par implants actifs; Evaluation of treatment with active implants in diabetes). EVADIAC monitors and gathers information into a computerized central registry.

The current implant, the MIP 2007 model (Medtronic-MiniMed, Northridge, CA, USA), underwent improvements to the electronic and battery components of the previous model. It has been in use since 2000 and has a 7- to 10-year battery life. Insulin delivery options are similar to those of the most up-to-date external pumps, and are programmable through a personal pump communicator (PPC). The catheter is inserted into the peritoneal cavity, while the pump itself is implanted in the abdominal wall. In 2007, the MIP 2007 device and Insuplant® 400 IU/ml (Aventis Pharma, Frankfurt, Germany), a semi-synthetic insulin used in implanted pumps, received marketing approval from the French regulatory agency. However, currently, Insuplant 400 IU/ml has been replaced by Insuman Implantable 400 IU/ml (Aventis Pharma), an ordinary recombinant insulin. As with Insuplant, this new insulin has been stabilized to prevent denaturation and precipitation in the implanted pump reservoir. The AMM is pending.

4.2. Clinical use

Observational clinical studies conducted by EVADIAC have clearly demonstrated the feasibility, metabolic efficacy and safety of the implanted pump in type 1 diabetic patients [38-41]. The metabolic benefits consist of a reduction in HbA1c, as well as in the frequency of severe hypoglycaemias and glycaemic variability. These benefits are maintained in the long term even in type 1 diabetics who remain far from the HbA1c target of 7% and/or have large blood glucose fluctuations, including severe recurrent hypoglycaemia, despite tight coaching and intensified education with SC insulin...
treatment [42]. A Dutch study [43] also showed that, with an implanted insulin pump, not only was HbA₁c significantly improved in those who were previously poorly controlled, but instability-related diabetic hospitalizations were also significantly reduced.

Several randomized clinical trials have compared the IP route with an implanted pump and the SC route with an external pump or multiple injections [44-47]. The most recent study [47] demonstrated significant improvement in glycemic control, expressed as a 0.8% decrease in HbA₁c over a period of 6 months when using implanted insulin pumps compared with SC insulin treatment in 24 poorly controlled diabetic patients.

The complications of treatment with implanted insulin pumps have clearly decreased over time and with user experience. These complications are mainly problems localized to the abdominal implantation site or due to under-delivery of insulin by the pump. Localized site problems dropped from 8 to <2 per 100 patient-years between 1990 and 2000 [41,48]. Usually, this represents localized infection [48,49] requiring temporary removal of the pump. Specific asepsis procedures and prophylactic antibiotics have helped to eliminate nearly all of these complications. Under-delivery of insulin results from either aggregation of insulin in the pump mechanism or obstruction of the peritoneal catheter. Insulin aggregation in the pump was linked to a defect in the Insuplant insulin that was then in use. The phenomenon is reversible in most cases by rinsing the pump with a soda solution. Its incidence has also dropped from 15 to <4 per 100 patient-years [39,41]. Other less common problems include electronic failure and premature battery depletion, which were recently reported to be 0.5 and 2.2, respectively, per 100 patient-years [42]. In addition, a higher rate of anti-insulin antibodies has been reported with implanted pumps, mainly in patients with elevated levels before implantation [50-52]. Many factors can cause this immunogenic response: the formulation of the insulin itself, the peritoneal route or, more likely, insulin aggregates in the pump mechanism have turned out to be highly immunogenic [53,54]. However, elevated levels of anti-insulin antibody have, in most cases, little effect on metabolic control in patients, although they have been described as blunting the plasma free insulin peak after a bolus, which can affect postprandial glycemic control [55]. On the other hand, extreme cases of “low morning syndrome” [50,51] have been reported due to the disabling combination of late-night hypoglycaemia and postprandial hyperglycaemia.

Nevertheless, compared with the metabolic benefits with implanted pumps in unstable type 1 diabetes patients, the rate of complications appears acceptable. The quality of life in patients treated with implanted pumps was assessed using validated questionnaires in some pilot studies [37,56], and revealed that patient satisfaction had significantly improved on switching from multiple injections or CSII to implanted pump therapy [37]. The impact of diabetes was also found to be significantly less in type 2 diabetic patients treated with implanted pumps [56]. A more recent study [47] reported better health-related quality of life and greater patient satisfaction with implanted pumps compared with SC insulin therapy. In addition to these quality-of-life evaluations, there is also the occasional patient’s testimony describing the benefits experienced with an implanted pump [57].

4.3. Indications

The current indications for an implanted pump are related to user experience and the metabolic benefits observed, and were presented in an EVADIAC “position statement” that has since been recently updated [58,59]. Treatment with an implanted insulin pump is indicated for type 1 diabetic patients with an HbA₁c >7% and/or presenting with large blood glucose fluctuations, including moderate and/or severe recurrent hypoglycaemic events despite intensified treatment with SC insulin.

4.4. Current use and perspectives

At this time, implanted insulin pump therapy is limited to a minority of selected patients based on who is likely to obtain the most benefit. There are currently 458 diabetic patients with an implantable pump: 370 in France, 3 in Belgium, 63 in the Netherlands and 22 in Sweden. The limitations of this treatment mode are the result of its technically specialized medical requirements, significant cost and reimbursement guidelines, as well as its limited manufacturing. Despite these limitations, however, the benefits provided to patients requiring this form of insulin therapy should be borne in mind.

The need to improve diabetes management to reduce the frequency, severity and consequences of hypoglycaemic events and degenerative complications constitutes a major public-health issue. Considering the health costs generated by the management of diabetes complications (such as hospitalization, work absences, medical transports, dialysis, retinal laser treatment, vascular bypasses and amputations), treatment with an implanted insulin pump should certainly constitute an acceptable cost and remain available when validly indicated.

Moreover, as regards implanted pumps coupled with glucose sensors, the implanted insulin pump is part of an innovative technology for diabetes and an important step towards the development of an artificial pancreas. Indeed, the pharmacokinetic properties [31,32] of IP-administered insulin give it a high reactivity that is of particular interest for use in a closed-loop system. Pilot studies have also shown encouraging results with implanted pumps coupled with intravenous [60] and SC [61] glucose sensors.

Thus, important advances have been made in the technology of insulin pumps, and the research is ongoing. The immediate expected patients’ benefits are accurate data, ease of use, and improvements in metabolic control, quality of life and compliance. The benefits to come are related to its implementation as a component of an artificial pancreas.
Conflicts of interest statement

The author has no potential conflict of interest relevant to this article.

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