Handbook of Diabetes Technology

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Foreword

It is very fitting that this timely book on diabetes technology should be written by a group of experts from France, since a paper by authors from that country published 44 years ago was highly influential in efforts to improve diabetes management, and in many ways was the beginning of what one might call the 'modern era' of technology in diabetes care. In 1974, French colleagues showed that up to 5 days of intravenous infusion of regular insulin from a pump held in a shoulder bag and given at a slow basal rate, augmented at meals, could achieve near-normoglycaemia in a small group of people with type 1 diabetes (Slama G et al. Diabetes. 1974;23:732–7). For the first time we saw that prolonged infusions of insulin are feasible and produce good glycaemic control without feedback control; and it suggested, at least to some, that portable pumps might be a technology for achieving strict glycaemic control in everyday clinical practice.

Building on these ideas over the next couple of years, continuous subcutaneous was substituted for continuous intravenous infusion in order to avoid the potential long-term problems of the intravenous route, the pump became a little smaller and 'insulin pump therapy', as it is now usually known, was introduced (from 1976), at first as an experimental treatment and then as an effective treatment option for type 1 diabetes. It is now used by more than one million people around the world with diabetes, so from this device alone one can say that technology forms a large part of current diabetes care.

These few years in the late 1970s and early 1980s saw the start of three other first-generation diabetes technologies that are now in common use, though in much more sophisticated versions: self-monitoring of blood glucose using portable meters and reagent strips in 1978, insulin 'pens' in 1981 and continuous glucose monitoring using an implanted electrochemical sensor in 1982. Since those early days, diabetes technology has taken more years to reach clinical maturity than many would have anticipated and liked, and faces some notable challenges even now. Foremost amongst these are variable and limited access for many of the patients who would benefit, and less than optimal use of some technologies like insulin pumps, as reflected in widely varying clinical outcomes in trials and in clinical practice.

One of the first things I was taught as a young doctor starting in diabetes research and clinical practice was that the biggest problem we face is putting into practice what we already know. Poor dissemination of information, lack of resources and lack of relevant practical skills have always hindered uptake of new treatments. But

technology probably plays a larger part in the care of diabetes than any other chronic disease, and this is surely set to continue, with increasing opportunities for automatic control of blood glucose (the 'artificial pancreas'), mobile connectivity and artificial intelligence. It has never been more important for diabetologists to know the best modern evidence for the effectiveness of technology, to understand which patients are best and most cost-effectively treated, and to appreciate both the advantages and the disadvantages of these new devices.

This book comprehensively addresses these issues and delves into much more besides: it summarises information on those diabetes technologies that are already in common and routine practice and those that are emerging—including external and implantable pumps, syringes and insulin pens, glucose meters, continuous glucose monitoring and closed-loop systems, the cell-based technology of islet cell transplantation, computer and software aids to education, data analysis, data logging, and decision support, mobile telephone apps, videogames and telemedicine.

It is a pleasure then to introduce this Handbook of Diabetes Technology and the chapters that follow. I am sure it will be of real practical help to very many healthcare professionals and students of diabetes. It is a substantial contribution to the understanding and successful application of technology in diabetes and thus to improving the care of people suffering from this condition.

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Preface

A comprehensive handbook browsing available resources related to diabetes technologies: glucose monitoring, devices for treating diabetes, telemedicine, software's and videogames! A helpful tool for physicians and nurses involved in the management of diabetes!

Caen, France — Yves Reznik

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About the Editor

Yves Reznik, MD is a Professor of Endocrinology, Diabetes and Metabolic Diseases at Caen University, Normandie, France. He is involved in the field of Diabetes Technologies and has an extensive experience with the management of insulin pump in type 2 diabetes. His team is involved in French and European closed-loop programs in type 1 and type 2 diabetes.

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Emmanuel Sonnet is hospital practitioner at the University Hospital of Brest (France) and qualified specialist in diabetology and endocrinology. He first studied and worked at the University of Rennes (France). His experience, area of interest, and recognized expertise are in the domain of the insulin pump therapy and new technologies in e-health (especially m-health).

Introduction to Diabetes Technologies

1

Pierre Yves Benhamou

For almost a century, diabetes mellitus has been at the crossroads of various technological innovations. The discovery of insulin (1922) was actually initiating the first therapeutic use of an extracted natural hormone, and this breakthrough was later followed by the first radioimmunological assay for the measurement of a circulating hormone (1960) and then by the first recombinant hormone ever produced (1978). These achievements led to several Nobel Prizes. Interestingly, all these biochemical innovations were later applied to other areas of medicine but were initially designed for the cure of diabetes. This first era of diabetes research ran from the 1920s to the 1970s and can be summarized as the "childhood years" where most of the pathophysiological and therapeutic basic concepts were described and established.

The second era, covering the 1980s to the early 2000s, introduced therapeutic concepts and tools that are still valid and explored nowadays: glucose self-monitoring, portable insulin pumps and implantable pumps, and insulin injection devices, all these landmarks were launched during this period. This is also true for other therapeutic breakthroughs, ranging from therapeutic education to cell therapy using islet transplantation or bioartificial pancreas. HbA1c was introduced in the 1980s, whereas the 1990s provided the first insulin analogs with pharmacokinetic properties that were more adapted to the therapeutic purpose. This era ended in 2000 with the introduction of the first continuous glucose monitoring system and the report of the first successful islet transplantation series. Yet these "teenage years," although astonishing by this firework of remarkable technological innovations that, overall, contributed to a significant improvement of diabetes care quality, failed to relieve patients from the daily burden of the disease.

We now stand in the third and hopefully last era. The "adulthood years" look as if history was speeding up its pace toward a cure. Continuous glucose monitoring without finger pricks is a reality. Closed-loop insulin delivery is expected to be

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marketed before the end of the decade. Islet transplantation is now routinely performed and fully covered in some countries, and insulin independence can reach up to 10 years. First clinical trials of bioartificial pancreas using embryonic stem cells have started in 2015. Diabetes scientific meetings are now attended by engineers, computer scientists, and big data experts. Social networks, communication technologies, smartphones, and connected devices are bridging patients, relatives, healthcare professionals, and researchers. Diabetes has entered a digital era (Table 1.1). Transdisciplinary approach among large international consortium has transformed the way research is conducted. Technology saves time, technology changes minds, and technology saves life. Therapeutic basic concepts have not significantly changed for decades, but improvements in technology (biotechnology, information technology, communication technology) have dramatically accelerated the availability of new and real therapeutic tools. In any case, what matters is the end of the road (Table 1.1): quality of life and cure are worthwhile, whereas every other outcome raises the question of human factor and alienation induced by technology. It is now reasonable to forecast that patients entering in the disease process now will have access to an online therapeutic education program featuring health games, as well as human resources through social networks involving dedicated healthcare professionals and expert patients. Patients will be presented with various therapeutic options, either multiple daily injections with connected smart pens and new ultrafast-acting insulin analogs or miniaturized insulin pumps. Freed from glucose monitoring burden, patients will be assisted by more and more accurate continuous glucose monitoring systems, which will soon be internal, invisible, and long-lasting devices. In both cases, therapeutic decision and dosing adjustment will be automatically managed and monitored remotely through artificial intelligence, with the assistance of various connected devices (physical activity trackers, pocket spectrometer for food analysis). This connected patient scenario is realistic for the coming decade. Meanwhile the most unstable patients will test the first bioartificial pancreas filled with human primary cells, then with xenogenic cells, and next with stem cells, announcing the liberation for the majority of patients. Real cure is within reach, hopefully not far from the first century after insulin discovery.

Table 1.1 Scenario for a cure

• The connected patient (<2020)
– Online therapeutic education
– Social networking with professionals and peers
– Automated monitoring (glucose, activity) with internal or invisible devices
– Miniaturized insulin delivery devices featuring artificial intelligence (artificial pancreas)
• The liberated patient (>2020)
– Bioartificial pancreas using allogenic islets
– Bioartificial pancreas using xenogenic islets
– Bioartificial pancreas using embryonic stem cells
– Bioartificial pancreas using autologous stem cells

Insulin Injection and Blood Glucose Meter Systems

2

Julia Morera

2.1 Insulin Injections

2.1.1 Insulin Injection Devices

2.1.1.1 Vials and Syringes

The first disposable glass syringe was introduced in 1954 and was quickly replaced by a plastic syringe. Since then, disposable syringes from several manufacturers have been in widespread use and there are three different sizes with a lineage easy to trace: 0.3 ml (30 U), 0.5 ml (50 U) and 1 ml (100 U) with dose increments of 0.5 or 1 U, 1 U and 2 U, respectively.

These syringes are available with 6 mm, 8 mm and 12.7 mm needles.

The syringe is a historical device which has gradually been supplanted by insulin pens, except in the USA, where syringes are still used by approximately 40% of patients taking insulin [1]. The decrease in syringe usage is mainly due to the inconvenience of carrying several materials and preparing the syringe for patients, the adverse psychological and social impacts of using a syringe, and failure to administer accurate doses (Table 2.1).

For cases of needle phobia, there is a specific device, Autoject® 2, in which an insulin syringe is integrated, allowing the user to hide the needle and automatically insert the needle and the contents of the syringe into the skin. This can be helpful in people suffering from a fear of needles.

2.1.1.2 Insulin Pens

Since the insulin pen was first manufactured in 1985, many improvements have been made to devices, leading to current pens with shorter and thinner needles,

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Table 2.1 Comparison of advantages and disadvantages of vial/syringes and reusable and prefilled insulin pens [2]

	Advantages		Disadvantages	
Vials and syringes	Reduced cost per unit of insulin Up to 100 U in one injection Half-increment dosing Patients can mix their own insulin formulations		More fear of injections Poor dose accuracy Lack of social acceptance Lengthy training time Difficulty of transportation No short needles	
Insulin pens	Ease of use Greater social acceptance/discretion of use Ease of portability Improved treatment adherence Less painful Short needles		Need for two injections in the case of high insulin doses (>60 or 80 U) Patients cannot mix their own insulin formulations Significant cost per unit of insulin	
	Prefilled insulin pen Easiest to use Lighter than a reusable pen	*Reusable insulin pen* Better environmental impact Possible memory function Half-increment dosing	*Prefilled insulin pen* Possible involuntary mixing between the long-acting and rapid-acting analog insulin pens	*Reusable insulin pen* Heavier than a prefilled pen

reduced injection force, color-coded insulin cartridges and packaging, and a built-it memory function [3].

These innovations have led to pen devices being used by approximately 60% of insulin users worldwide [4], though there are disparities between different countries: in European countries, Japan, China and Australia, pen devices are used by 95% of insulin users, whereas in the USA, they are used by only approximately 60% of patients [1].

Patients prefer the pen devices to vials and syringes, stating advantages such as ease of use (even in cases of impaired vision or compromised manual dexterity), convenience, greater confidence in their ability to properly administer the drug, less pain and less needle fear, and greater perceived social acceptance [2, 3], especially if they feel encouraged by their physicians to use a pen [5]. Patients also seem to take less time to learn to inject themselves with a pen compared with a syringe [2].

Insulin analogs supplied in cartridges or prefilled pens have a higher per-unit insulin cost than do insulin analogs supplied in vials [6], but a review [7] showed that use of pen devices was associated with improved adherence to insulin therapy and in this way reduced diabetes care costs compared with vials and syringes [6, 7].

Prefilled Versus Reusable Insulin Pens

There are two types of insulin pens:

– Reusable insulin pens which are designed for use with 3-ml prefilled insulin cartridges and are listed in Table 2.2 (nonexhaustive data). These pens may be preferred for environmental reasons but also in pediatric populations and in

Table 2.2 List of reusable insulin pens actually marketed (nonexhaustive data)

	Traditional reusable insulin pens													Connected reusable insulin pens		
	ClikStar	JuniorStar	HumaPen Luxura HD	HumaPen Savvio	HumaPen Memoir	NovoPen® 4	Novopen® 5	NovoPen® Echo	Diapen Softpen	I-pen	AutoPen	AutoPen24		DataPen	SmartPlus Digital	VigiPen®
Pharmaceutical laboratory	Sanofi		Lilly			Novo Nordisk			Haselmeier		Owen Mumford			Biocorp	SmartPlus	Vigilant
Insulin	Glargine Glulisine		Humuline Lispro Biphasic lispro			NPH Aspart Biphasic aspart Detemir			All insulin		Sanofi cartridges	Lilly cartridges		All insulin cartridges	Sanofi and Lilly cartridges	Rechargeable VigiPen® cartridges with all bottled insulin
Max units (U)	80	30	30	60		60		30	58	60	21	42	21 42	ND	60	21
Min units (U)	1	1	0.5	1		1		0.5	1	1	1	2	1 2	ND	0.5	1
Dose increment (U)	1	0.5	0.5	1		1		0.5	2	1	1	2	1 2	ND	0.1	1
Duration of press on button (s)	10		5			6			ND		10		10	ND	ND	ND
Specific features	–	–	–	–	Memory function Display	–	Memory function Display	Memory function Display	Automated needle insertion and dose delivery Hidden needle	–	Automated dose delivery at touch of button		–	Software: ND	Software: DiabeticPlus (Apple or Google Play)	Software: VigiHealth app (Apple or Google Play)

Max maximum, *Min* minimum, *ND* no data, *NPH* neutral protamine Hagedorn (isophane)

patients with small insulin requirements because some of them offer the possibility for half-increment dosing.
– Prefilled insulin pens which contains 3 ml of insulin and are listed in Table 2.3.

The choice of insulin pen essentially depends on the choice of insulin and on the patient's preferences (Table 2.1).

Accuracy of Dosing and Force Required for Insulin Injection

All insulin pens meet International Organization for Standardization (ISO) 11608-1:2000 standards for dose accuracy at 1 unit: the calculated statistical tolerance limit should not deviate from the target dose by more than 1 unit for the delivery of 5 units and not by more than 5% for the delivery of 30 U and 60 U [8].

Several studies have investigated dosing accuracy among pens and have demonstrated consistent and accurate dose delivery for prefilled and reusable insulin pens according to the ISO recommendations, without clinically relevant differences among the products [9–12].

The force required to inject an insulin dose can also differ between insulin pens, but the study results are conflicting and the observed differences seem relatively small [4, 13–15].

Needle Features

Pen needles come in lengths ranging from 4 to 12.7 mm.

Reduction of needle wall thickness allows the insulin flow to be increased at a constant thumb force, leading to performing an insulin injection more easily and

Table 2.3 List of prefilled insulin pens

	SoloStar®	FlexPen®	FlexTouch®	Innolet®	Kwickpen®
Pharmaceutical laboratory	Sanofi	Novo Nordisk			Lilly
Insulin	Glargine Glulisine	Detemir NPH Aspart Biphasic aspart		Detemir NPH	Humuline NPH Biphasic humuline Lispro Biphasic lispro
Max units (U)	80	60	80	50	60
Min units (U)	1	1	1	1	1
Dose increment (U)	1	1	1	1	1
Duration of press on button (s)	10	6	6	–	5
Features		A dose larger than that remaining in the pen is not possible	Low injection force End-of-dose click	Specifically developed for people with poor eyesight or reduced manual dexterity	

Max maximum, *Min* minimum, *NPH* neutral protamine Hagedorn (isophane)

quickly. Extra-thin-wall needles (4 and 5 mm) have been developed and patients who have tested them reported a significant preference for these needles, describing reduced thumb force, reduced pain and a decreased time to deliver insulin [16].

Furthermore, the 4- or 5-mm needles have a lower risk of intramuscular injection [17] (Fig. 2.1) and they provide glycemic control equivalent to that of the longer needles, even in obese patients, without an increase in leakage [18–20]. In Europe, 63% of adult patients on insulin treatment were using an 8-mm or longer needle [21]. Future guidelines will recommend greater use of shorter-length pen needles for patients with diabetes.

Trends in Insulin Pen Development

The current trend is the development of insulin pens with an electronic dose display and a memory function. These devices allow the user to record insulin doses and the date(s) and time(s) of the last injection(s), but there is actually no proof that use of this device is associated with an additional improvement in glycemic control [22]. This function can be particularly useful in younger patients in whom insulin is administered by multiple caregivers and it may help reduce the risk of double injections or provide parents with information on a child's adherence to treatment. In a pediatric population, 89% of patients evaluated this function as having good ease of use [23].

In the future there will probably be marketing of connected insulin pens which will, in connection with a mobile application via Bluetooth, allow the patient to track his treatment, improve his adherence and send his data to his doctor (Table 2.2). Alerts indicating forgotten or inadequate-dose injections could also be an interesting option, since an increase in hemoglobin A1c (HbA1c) of 10% has been estimated for every four missed meal boluses per week in pediatric patients, and an HbA1c effect of −0.5% for only two boluses per week not missed has been estimated [24]. These devices have not yet been evaluated.

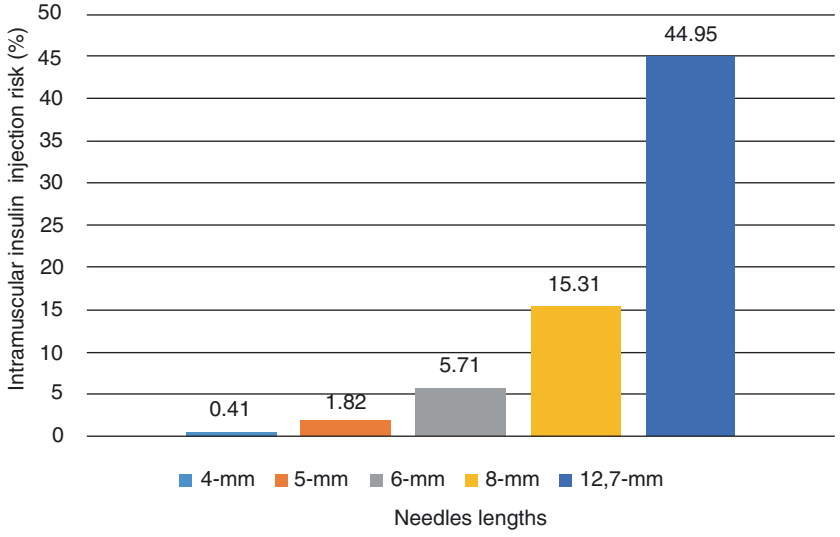

Fig. 2.1 Risk of intramuscular insulin injection as a function of the length of pen needles (according to [17])

Medical Devices Associated with Insulin Pens

- Tracking of the Last Injection

There is a smart cap (Timesulin™) that can be placed onto the insulin pen and can display when the last insulin injection was administered. This device is compatible with almost all refillable insulin pens.

- Connected Devices

Medical devices that adapt to insulin pens (Bee™, EasyLog™) are in development and allow the user to record the injected insulin doses and to send these data to a mobile application in order to note them in a glycemic logbook. These devices are compatible with almost all reusable and prefilled insulin pens. However, the glycemic results have to be manually noted in the logbook.

In the future this kind of device will probably be connected to the blood glucose (BG) meter in order to automatically transfer and record the insulin doses and the glycemic data in the same logbook.

- Devices for Use in Cases of Needle Phobia

There are several specific devices with a hidden needle allowing the user to perform insulin injections in people suffering from a fear of needles:

– BD Autoshield™ Pen Needle (BD; 5 or 8 mm) and NovoFine® Autocover (Novo Nordisk; 8 mm) are pen needles which are applied to the skin, allowing the shield to retract and the hidden needle to penetrate the skin. These devices are compatible with all insulin pens.
– Novopen® 3 PenMate® (Novo Nordisk) is a device which is screwed onto the body of the insulin pen and wherein an insulin cartridge is inserted. The pen needle is hidden by the device and penetrates the skin after pressure on the body of the insulin pen. It is only compatible with old reusable insulin pens (NovoPen® 3, NovoPen® 3 Demi, NovoPen® Junior) and NovoFine® pen needles.

2.1.1.3 Insulin Injector

By using a compressed gas cartridge or a compressed spring, needle-free insulin administration devices, such as InsuJet™ and Injex30™, push the insulin at high speed through a small orifice, creating a fine stream of insulin that penetrates the skin (transdermal administration) then diffuses in the subcutaneous tissue. These devices have been developed for needle-phobic diabetic patients.

In healthy volunteers, it has been shown that a jet injector greatly enhances the rate of insulin absorption and reduces the duration of the glucose-lowering action, in comparison with conventional insulin administration, when using insulin aspart [25] or insulin lispro [26], but there has been no study with long-acting insulin analogs.

In a small pilot study of ten patients with type 1 diabetes (T1D), the administration of insulin aspart by an injector had the same effect on the glucose profile as conventional insulin administration and this device was rated similarly for participant preference and relative injection pain [27]. There has been no more extensive study.

The large size, the very high pressure required and the pain induced are reasons why this kind of device has never been a commercially reality. Another limitation is the cost: limited reimbursement in the USA has deterred many from trying these devices, while in Europe these devices have not been widely promoted within public health systems, except in the UK.

2.1.2 Injection Technique

2.1.2.1 Practical Aspects

Syringes and pen needles have to be used only once in order to limit the risk of infection and appearance of air bubbles which can lead to underdelivery of insulin. Furthermore, a higher rate of needle reuse has been identified as an independent risk factor for lipohypertrophy [28].

Pens must be primed before each injection with 2 units of insulin in order to displace any air in the needle and to ensure an accurate injection avoiding underdelivery of insulin, even if the pen needle is changed.

For an insulin pen, the needle should be embedded within the skin for several seconds after complete depression of the plunger to ensure complete delivery of the insulin dose. In cases of premature needle withdrawal after injection, there may be a non-negligible amount of insulin not delivered (up to 20% of the selected dose) and this can be critical for subjects with low insulin needs [29], but this phenomenon can be avoided by keeping the needle in the skin as recommended by the manufacturer (Tables 2.2 and 2.3).

2.1.2.2 Injection Sites

Insulin injections have to be administered in subcutaneous tissue (in the abdomen, buttocks, lateral sides of thighs and upper arms). Intramuscular injection should be avoided due to the risk of severe hypoglycemia [30]. Since the 4-mm pen needles were introduced, other insulin injection sites have been explored and the upper inner thigh might be another option [31].

Site rotation is essential to avoid lipohypertrophy and ensure consistent absorption of the insulin. Patients should be taught a personalized "structured rotation" for their injection sites.

Structured rotation is recommended in the same anatomical region at the same time of day with the injections being at least 2–3 cm apart (two fingers) across the entire area (Fig. 2.2).

2.1.3 Conclusion

The evolution of insulin devices has allowed us to improve patients' comfort and technological advances now make it possible to personalize the choice of assistance devices for each patient, while ensuring better performance on the part of these devices. In the future, connected and painless devices will probably be developed and should be made available to patients to improve their adherence to antidiabetic treatments.

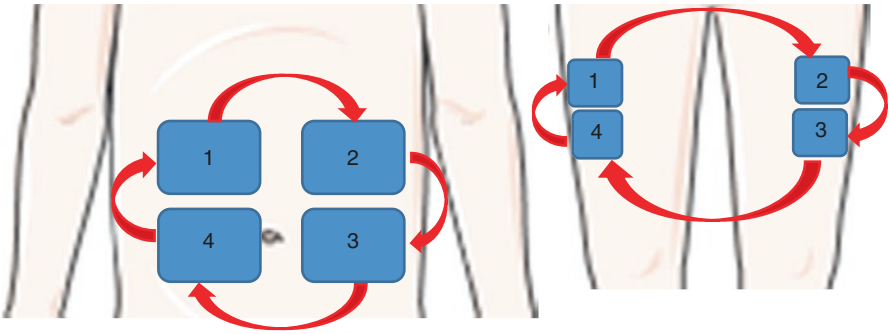

Fig. 2.2 Sample structured rotation plan for injections in the abdomen and thighs: divide the injection side into quadrants or halves, use one section per week and move clockwise. Injections within any quadrant should be spaced at least 2–3 cm from each other

2.2 Blood Glucose Meter Systems

Self-measurement of blood glucose (SMBG) is an essential element in the treatment of patients with T1D and insulin-treated type 2 diabetes (T2D), allowing the patient to adjust insulin therapy in order to have tight glycemic control and avoid late complications [32, 33]. Its use is more controversial in non-insulin-treated patients with T2D but can help to evaluate the efficacy of hypoglycemic treatments and play an educational role for patients [34, 35].

Since the first BG meter was manufactured in 1970, many improvements have been made, leading to the current BG meters which have become lighter, faster in determination of glucose values, easier to use, with a reduced deposit volume needed to determine capillary BG.

In parallel, lancing devices have been modernized, becoming less painful, mainly for obtaining a lesser quantity of capillary blood (0.3–0.5 μl) [36].

2.2.1 Principle of Glucose Detection

Glucose meters have two essential parts: an enzymatic reaction and a detector. The enzyme portion of the glucose meter is generally packaged in a rehydrated state in a disposable strip. Glucose in the patient's blood sample rehydrates and reacts with the enzyme to produce a product that can be detected. There are two principal enzymatic reactions utilized by glucose meters: glucose oxidase (GO) and glucose dehydrogenase (GDH) [37].

The GO method involves the oxidation of glucose to gluconic acid by GO, forming hydrogen peroxide. This reaction is not completely specific for glucose and can give falsely low results with high oxygen content or substances such as uric acid, ascorbic acid, bilirubin, hemoglobin, tetracycline and glutathione [38].

The GDH method involves the oxidation of glucose to gluconolactone by GDH, forming reduced nicotinamide adenine dinucleotide (NADH) [38].

All meters are susceptible to heat and cold because the enzymes can be denatured and become inactivated at extreme temperatures. Test strips should not be stored in closed vehicles for extended periods and must be protected from rain, snow and other environmental elements [39].

A number of factors can cause erroneous readings on BG meters and these aspects have to be take into account in order to choose the best BG meter for each patient:

- With the GO method of detection, an increase of the glucose reading can be observed in the case of anemia, low oxygen content, alkalosis or overdose of paracetamol, while a decrease can be observed in the case of polycythemia, high oxygen content, acidosis or overdose of uric acid, ascorbic acid or tetracycline.
- With the GDH method detection, an increase of the glucose reading can be observed in cases of anemia, products containing xylose, hyperbilirubinemia or overdose of paracetamol, while a decrease can be observed in cases of polycythemia, hypercholesterolemia (>11 g/l) or hypertriglyceridemia (>47 g/l) [39].

However, these factors actually have little bearing in the average patient with diabetes mellitus, and human misuse of the BG meter has been found to be a more significant source of error than the instrument itself [40].

2.2.2 Accuracy and Security

2.2.2.1 Technical Accuracy

Technical accuracy is defined as the measurement closeness of agreement between a measured quantity value and a true quantity of glucose. This criterion is different from precision which describes the reproducibility of a series of values, independent of the closeness of any of the values to the reference (Fig. 2.3) [39]. Only when a series of values is both accurate and precise do the individual values reflect the reference value.

There are a number of factors that can influence the accuracy of BG strips [39]:

- Variation of the strip's quality between different manufactured lots
- Influence of altitude
- Influence of extreme temperature
- Variation of the hematocrit level which can change the glucose reading but can also block the electrode or the enzyme of the strip and alter the reading
- Patient technique
- Use of some medications

Fig. 2.3 Accuracy and precision of glucose meters. In *each panel*, the *center of the circle* represents the reference value. In the *left panel*, the individual values have a mean value that is the same as the reference value, defining the accuracy. In the *center panel*, all values are nearly identical, defining the precision. In the *right panel*, the set of values is both accurate and precise [39]

2.2.2.2 Clinical Accuracy

While technical accuracy refers to the analytical result agreement of a BG meter with a comparative laboratory method, clinical accuracy compares the medical decisions based on the test results.

Clarkes [41] and then Parkes [42] established error grid analysis in order to evaluate SMBG methodologies and verify the clinical significance of the BG meter result against a comparative method. These error grids have five accuracy categories: zones A and B for when we can see a mild discrepancy between the glucose meter result and the comparative method, resulting in no change in the clinical decision; and zones C, D and E for when we can see larger differences between the glucose meter and the comparative method, resulting in unnecessary corrective action or potentially dangerous failure to detect hypoglycemia or hyperglycemia (Fig. 2.4).

2.2.2.3 Meter Performance Criteria

Manufacturers of glucose meters have to provide evidence of conformity with the ISO 15197:2013 standard [43] which defines the following performance requirements for glucose meters:

- The standard states that ≥95% of the BG system measurement results shall fall within ±15 mg/dl of the results of the manufacturer's measurement procedure at glucose concentrations <100 mg/dl and within ±15% at glucose concentrations ≥100 mg/dl.
- Ninety-nine percent of individual glucose results shall be included in zones A and B of the Parkes error grid.
- Evaluation of interferences is mandatory, with a list of 24 substances which need to be tested. The influence of the hematocrit on the glycemic level shall also be studied.

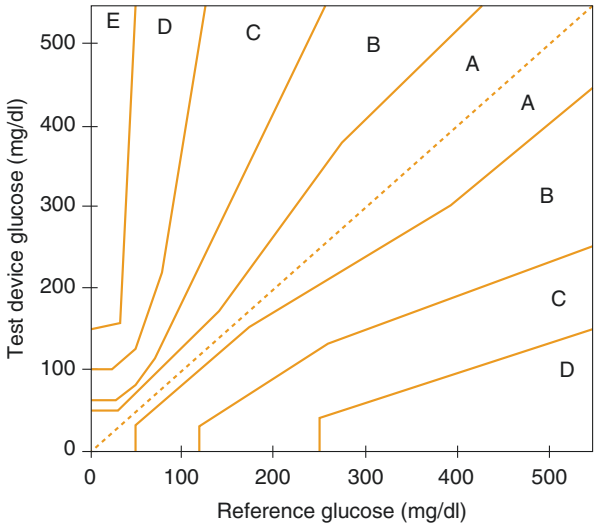

Fig. 2.4 Parkes error grid. The error grid is divided into zones signifying the degree of risk posed by incorrect measurement: A: no effect on clinical action; B: altered clinical action or little or no effect on clinical outcome; C: altered clinical action—likely to affect clinical outcome; D: altered clinical action—could have a significant medical risk; E: altered clinical action—could have dangerous consequences [42]

2.2.3 Criteria for Choosing a Glucose Meter

Some examples of BG meters are listed for each selection criterion, but the list is not exhaustive. Depending on the country, the names of BG meters may be different from those used in this text.

2.2.3.1 Patients with Type 1 Diabetes

Use of an Automated Bolus Advisor

Bolus insulin calculation requires individuals to utilize several factors such as insulin to carbohydrate ratios, the insulin sensitivity factor, target BG range, current BG values and anticipated physical activity. This calculation can be problematic in individuals with deficits in literacy and numeracy, and can be replaced by an empirical estimate of the insulin need because the calculation is complex and time consuming. The use of an automated bolus advisor can facilitate improvements in glycemic control without increasing hypoglycemia, improve treatment satisfaction, reduce dosage errors, assist in improving carbohydrate counting competence and reduce fear of hypoglycemia [44]. Only the FreeStyle Papillon® InsuLinx BG meter (Abbott) has this device.

Blood Ketone Detection

Measurement of whole-blood or urinary ketones plays an important role in the management of diabetes ketoacidosis. Ketone meters are often available in emergency rooms but can be prescribed to patients with brittle glycemic control in order to detect, as early as possible, the presence of ketones in the case of hyperglycemia and start corrective measures.

This ketone meter concerns patients with T1D exposed to a ketoacidosis risk—in particular:

- Children and teenagers
- Patients treated with an external or implantable insulin pump
- Pregnant diabetic women
- Young patients with behavioral disorders that can lead to noncompliance with insulin therapy [45]

The FreeStyle Optium® Neo meter (Abbott; FreeStyle Optium® β-ketone strips) and the Glucofix® Premium meter (Menarini; Glucofix® β-ketone sensor strips) are BG meters using this function.

Connection with a Subcutaneous Insulin Pump

Use of an automated insulin pump and meter seems to increase the daily frequency of BG testing in youth patients with T1D [46].

The Contour Next® Link meter (Bayer) connects to the Medtronic MiniMed® Real-Time and MiniMed® Veo pumps and the Contour Next® Link 2.4 m connects to the Medtronic 640G® pump. These BG meter can directly transfer the glycemic results to the pump and, in some cases, be used to program a bolus. The uploading of pump data also allows a display of insulin doses and BG results in the same graph or the same table (see example using the Contour Next® Link BG meter and the MiniMed® Veo pump in Fig. 2.5).

2.2.3.2 Patients with Type 1 Diabetes or Type 2 Diabetes Receiving Multi-daily Insulin Injections

Presence of a Logbook in the Blood Glucose Meter

This device can help patients to fill out a correct glycemic book (FreeStyle Papillon® InsuLinx BG meter). Indeed, we know that in one study only 58% of people with T1D reported they performed at least three tests a day [47] and all these results are not always recorded in a glycemic book or are not in agreement with the meter memory in 50% of cases, because of underreporting, lack of concordance or overreporting [48].

No Strip

SMBG is time consuming which can decrease the frequency of BG testing.

The Accu-Chek® Mobile (Roche) is an all-in-one meter and allows the user to perform BG measurement faster and more easily. Indeed, the single strips are eliminated, with 50 strip-free tests on a continuous tape and the integrated lancing contains six lancets in a drum, requiring only four steps to perform a test.

The FreeStyle Libre® (Abbott) is a continuous glucose monitoring device coupled to a meter able to scan and store glycemic results. This system allow the user to know the glucose level without a strip or lancing device. It is faster and more painless than traditional SMBG.

Alarm Function

BG meters can have an alarm function in order to remind the patient to perform a BG measurement (FreeStyle Papillon® BG meters, Contour BG meters, Accu-Chek® BG meters, Glucofix® Tech meters, etc.). This can be useful for patients who tend to forget to measure their capillary glycemic level. There are two types of alarms:

- A postprandial alarm function to inform the patient that it is time to measure their postprandial glucose level
- A programmable alarm that is set by the patient for the desired time

Connection with a Smartphone

Some BG meters can be connected with a smartphone. Free downloaded apps are needed in order to edit the glycemic data in logbooks, tables or graphs and statistic reports, and these reports can be sent to the user's physician by email. The transfer of data is possible either when the BG meter and smartphone are physically connected or via Bluetooth transmission. The following are some BG meters:

- iBGStar® meter (Sanofi) which connects to an iPhone or iPod only and requires the iBGStar® Diabetes Manager application, only available from the Apple Store
- Glucofix® Tech meter (Menarini) which connects to a smartphone (or tablet) and requires the GlucoLog® Lite or GlucoLog® Mobile applications, available from the Apple Store or Google Play
- OneTouch Verio® Flex meter (LifeScan) which connects to a smartphone (or tablet) and requires the OneTouch Reveal® application, available from the Apple Store and Google Play

Continuous Glucose Monitoring

The FreeStyle Libre® is based on a flash glucose monitoring system. It uses a small sensor which automatically measures and stores the glucose results, coupled to a meter which reads the glucose result by scanning even through clothing. The sensor is small (35 mm × 5 mm), is water resistant, is applied on the body once every 2 weeks and does not require finger pricks for calibration. With every scan, the current glucose reading is obtained but also an arrow showing the glycemic trend and the last 8-h of glucose data are shown as a graph. The system stores up to 90 days of glucose data.

The performance of this system was demonstrated in a study showing accuracy in comparison to capillary BG reference values and stability of accurate readings over 14 days of use, and the percentage of readings within consensus error grid zone A was between 85.2% and 89.2% [49].

The data can be transferred to a computer via FreeStyle Libre® software and are summarized as a graph (Ambulatory Glucose Profile).

2.2.3.3 Patients with Type 2 Diabetes Receiving Multi-daily Insulin Injections or Only Basal Insulin

Assistance in Interpretation of Results

BG meters offer the possibility to help the patient to interpret his glycemic result, either:

- With an alert in the case of hypo- or hyperglycemia (BGStar®, Sanofi; OneTouch Verio® and OneTouch Verio® Flex; AutoSense®, Aximed).
- With an indication of a glycemic trend over several days. This indication can be noted by trend arrows (FreeStyle Optium® Neo; MyStar® Extra, Sanofi) or by a color code (OneTouch Verio® IQ, LifeScan). One study compared the efficacy of the self-management performance of two color-indication methods, with one group of patients recording their BG levels on the note manually and marking high and low levels with red or blue pencil, respectively, and another group using a BG meter with color-coded indicator lights (red, orange, green and blue lights) signifying BG levels [50]. The manual color record seemed to have a favorable effect, resulting in improved glycemic control and suggesting active usage of the glycemic results.

2.2.3.4 Non-insulin-treated Patients with Type 2 Diabetes and Patients with Gestational Diabetes

Almost all patients look for simplicity of use and prefer BG meters which do not require calibration. The criteria for choice are more oriented toward BG meter design, size or simplicity of use.

2.2.3.5 Other Criteria for Choice of Meters

Eye Disorders

If the disease is moderate, it can be useful to focus on a BG meter with a large screen and large displayed letters (FreeStyle Papillon® Vision, Abbott; Glucofix® Premium and Glucofix® ID, Menarini; Accu-Chek® Performa, Roche) or with a display backlight (OneTouch Verio®; BGStar®; MyLife® Pura, Yposmed).

In the case of blindness, a talking BG meter can allow the patient to perform glucose measurement by vocalizing each step of the glucose test (AutoSense® Voice, Aximed; Vox®, Os Care). Clear and simple sentences expressed by a human voice indicate the process and guide users from the beginning to the end of the test and clearly set out the results. Different languages are available for each BG meter.

Gripping Disorders

Patients will prefer big BG meters using large and rigid strips, such as MyLife® Pura. The Accu-Chek® Mobile BG meter can also be useful because the operations can be done with only one hand.

In these patients, the use of lancing devices for single use can facilitate obtaining a blood drop (BD Microtainer® lancets, BD; Unistik® 3 Gentle lancets, Owen Mumford). Indeed, these lancing devices are often large, easy to use and usable with one hand because they simplify the test.

Use of Alternative Sites

The majority of BG meters offer the possibility to perform capillary glycemic measurement at different sites, such as the base of the thumb, forearm, upper arm, thigh and calf (Fig. 2.5), allowing the fingertips to be rested.

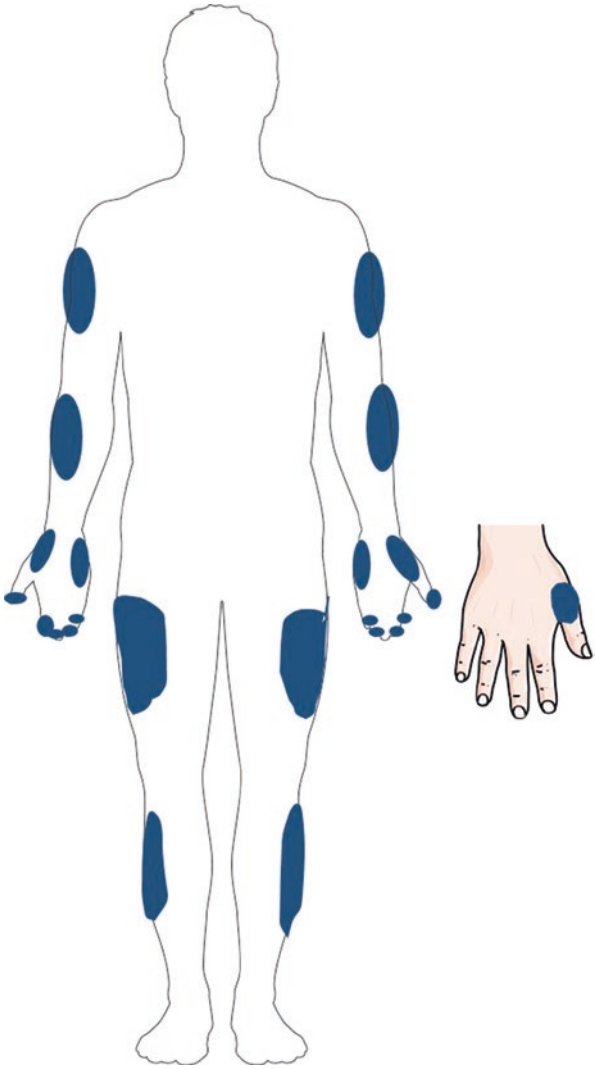

Fig. 2.5 Alternative sites for the capillary glucose test

Batteries
The energy consumption by BG meters is uneven and depends on the patient's use. The number of batteries differs between BG meters: one or two lithium batteries or two AAA batteries. Some BG meters can be recharged by mains connection.

Storage Capacity and Calculation of Mean Blood Glucose
All BG meters have storage capacities (from 250 to 2000 tests) and almost of them offer the possibility to calculate the mean BG level over the last 7, 14, 30, 60 or 90 days, but these criteria do not seem to be very discriminating factors.

2.2.4 Data Management

All BG meters offer a download function for collecting the glucose data stored in memory, allowing the user to:

- Create a custom folder
- Edit reports, tables and graphs from the downloaded data
- See the glycemic logbook over fixed periods
- Store virtually unlimited data
- Send data to the doctor

Almost all glucometers allow the user to manage the data with specific software which is freely available for download or directly integrated into the BG meter. Connection of the BG meter to the computer can be done by use of a USB cable (which can be attached to a USB port on the BG meter) or infrared adapter (which may or may not be free and is available to order online or included in the BG meter kit).

Some BG meters can be connected to a smartphone via a mobile application to manage the stored data (see above).

There is also nonspecific data management software available for purchase. It is compatible with almost BG meters and some insulin pumps:

- Diabass® software (compatible with PC)
- Sidiary® software (compatible with PC and with Android, iPhone and Windows phones)
- Diasend® software (compatible with PC and Mac)
- Glooko® software (compatible with Android, iPhone and Windows phones)

2.2.5 Conclusion

The self-measurement of blood glucose that has developed during the past three decades has become an essential part of the treatment of diabetes mellitus. The evolution of blood glucose meters has allowed us to improve patients' comfort and

technological advances now make it possible to personalize for each patient the choice of assistance devices, while fulfilling the greater performance requirements of these devices.

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Subcutaneous Insulin Pumps

3

Yves Reznik and Emilie Deberles

3.1 Definition and Principles of Insulin Pump Technology

Insulin pumps are devices which insure the delivery of a pre-programmed amount of insulin over 24 h. It uses a small portable electrochemical pump and is composed of a reservoir containing an amount of insulin (1.5–3 ml of insulin at 100 U/ml) which is infused via a flexible plastic tube and a cannula inserted into the subcutaneous tissues. Pumps deliver continuously over 24 h small amounts of insulin as micro-boluses every few minutes. Only rapid-acting insulin analogues are administered by pumps in two different patterns: (1) a pre-programmed amount of insulin delivered continuously corresponding to the basal rate and (2) an amount of insulin delivered in a shot corresponding to the immediate insulin need for food eaten or high glucose correction. Pump advantages over multiple daily injections (MDI) lie in their ability to deliver tiny amounts of insulin tailored for each daytime or nighttime period in order to finely tune the insulin pharmacokinetics to individual's requirements. Therefore, planned and immediate adjustments can be made to insulin delivery, such as overnight increase in insulin rate delivery to prevent the dawn phenomenon or decrease in insulin infusion rate after a bout of physical activity.

3.2 Clinical Evidence for Using Pump Therapy

3.2.1 In Type 1 Diabetes

Continuous subcutaneous insulin infusion (CSII) was first used in the 1970s [1, 2]. Observational studies have compared the efficacy of pump therapy after switching

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from MDI to pump. All studies performed in adults have shown a significant reduction in HbA1c ranging from −0.2 to −1.4% when patients were switched to pump [3]. The Cochrane review on pump use in adults with T1D has shown an advantage of pump therapy over MDI on glucose control with a −0.3% HbA1c decrease (95% CI, −0.1 to −0.4). Pump efficacy compared to MDI was higher in short-time studies (<6 months) than in longer studies [4]. A recent meta-analysis of randomized controlled trials (RCTs) comparing pump to MDI has confirmed a higher HbA1c reduction of −0.30% with pump [5]. Baseline HbA1c was proven to be a major determinant of pump efficacy over MDI in a large Swedish survey: subjects with an HbA1c at 9% had a greater HbA1c reduction with pump in comparison to patients on MDI than those with a baseline HbA1c of 7% and 8% (−0.25% vs −0.08% and −0.16%, respectively) [6]. Pump therapy use also helps to reduce blood glucose variability in comparison with long-acting and rapid-acting MDI [7]. A meta-analysis comparing the rate of severe hypoglycemia in 22 studies including 6 RCTs showed a 4.19 higher rate of severe hypoglycemia on MDI compared to pump, such ratio being 2.89 for the sole RCTs [8]. Pediatric studies have shown contrasting results. Reports from two large pediatric registries from Germany and the United States evaluated the outcomes of children less than 6 years old, the former showing significantly lower mean HbA1c on CSII than on MDI but the latter failing to demonstrate such advantage [9]. Long-term use of CSII in 345 children has shown better glycemic control than matched children on MDI, with a mean HbA1c difference of −0.6% which was maintained throughout the 7 years of follow-up [10]. The use of more recent tubeless insulin pump therapy in children was also associated with better glycemic control compared to MDI therapy [11]. In a recent study among 223 young adults with type 1 diabetes transitioning from the pediatric care, the use of CSII was associated with lower glucose variability measured by CGM and lower overall hypoglycemic events than MDI during a 2-year period of follow-up [12]. In a socioeconomic point of view, pump use in children is linked to parent's education and income levels [13]. An important issue remains whether pump therapy is protective against long-term diabetes complications. In a meta-analysis of 24 RCTs involving 9302 patients, Virk et al. have observed that incident retinopathy was reduced by 55% in pump users compared to MDI independently from HbA1c level [14]. A prospective cohort study on 989 subjects with type 1 diabetes has also shown a lower rate of retinopathy and neuropathy (odds ratios 0.66 and 063, respectively) associated with the use of pump therapy compared to MDI in a multivariate analysis [15]. Recent studies have shown that pump therapy in comparison with MDI was able to reduce proteinuria independently from HbA1c reduction after 1-year utilization [16, 17]. The long-term effect of pump therapy on cardiovascular risk was studied in a Swedish observational survey comparing 15,727 subjects on MDI to 2241 subjects on pump therapy. The authors have observed after a 6.8-year follow-up a significant reduction of cardiovascular events in subjects using pump, with adjusted hazard ratios for insulin pump of 0.55 (95% CI, 0.36–0.83) for fatal coronary heart disease, 0.58 (95% CI, 0.40–0.85) for fatal cardiovascular disease, and 0.73 (95% CI, 0.58–0.92) for all-cause mortality [18]. Recently, a large population-based cohort study

performed in European countries has compared 9814 patients using pump therapy with the same number of MDI users. Pump therapy compared to MDI was associated with lower rates of severe hypoglycemia and diabetic ketoacidosis together with better glycemic control [19].

Pump therapy may be offered to pregnant women with type 1 diabetes. A recent meta-analysis concluded that pump therapy use compared to MDI resulted in better first trimester glycemic control, this difference decreasing in the subsequent trimesters. Pump therapy was associated with lower insulin requirements but larger weight gain in mothers and with greater risk of large for gestational age but lower risk for small for gestational age [20].

3.2.2 In Type 2 Diabetes (T2D)

Few RCTs compared the effectiveness of CSII versus MDI before 2014 and have drawn contrasting conclusions. These studies compared small samples of subjects and did not compare pump to MDI with rapid- and slow-acting insulin analogues [21–24]. The OPT2MISE study was the first large multicenter randomized study comparing pump therapy to MDI with optimal basal-bolus therapy and high insulin requirements (total daily dose > 0.7 U/kg/day) in 331 T2D subjects with poor glycemic control (HbA1c > 8%). After 6 months, HbA1c was reduced by −0.7%, and insulin requirements were reduced by −20% in the pump group compared to MDI. There was no difference in body weight gain, and the time spent in hypoglycemia recorded by CGM was similar in both groups [25]. The beneficial effect of pump therapy was maintained after 1 year of pump use [26]. Observational studies have also shown pump superiority over MDI, a recent report showing the sustained efficacy of pump therapy in a cohort of 161 T2D subjects who failed to respond to an intensive MDI regimen, with a −1.3% HbA1c decrease from baseline after 1 year of pump therapy and maintenance of this effect over a mean period of 6.8 years [27].

3.3 Clinical Use of Pump Devices

3.3.1 Patient's Selection

According to the NICE guidelines, pump may be offered to adults and children with type 1 diabetes: (1) who are unable to reach an HbA1c target below 8.5% (69 mmol/mol) with an intensified MDI regimen including rapid-acting plus long-acting insulin analogues, (2) who have experienced severe hypoglycemia or repeated disabling hypoglycemia altering their quality of life, and (3) who are pregnant and cannot reach the adequate glycemic and HbA1c targets despite an intensified MDI regimen [3]. These indications of pump therapy have been proven cost-effective. Among children with type 1 diabetes, pump may be indicated when MDI are inappropriate or impractical. The AACE consensus has stated that pump therapy may be indicated(1) when HbA1c is above 7% (53 mmol/mol), (2) when

there are increased blood glucose fluctuations before meals, and (3) when there is dawn phenomenon with fasting glucose above 200 mg/dl (11 mmol/L) uncontrolled by an MDI regimen [28]. Other possible indications are recurrent ketoacidosis, hypoglycemia unawareness, unwillingness to perform multiple injections, and personal preference. Due to high cost of pump therapy, pump advantage may be balanced to cost issues on an individual basis. Moreover, the typical pump user may be one engaged in self-managing his diabetes, adjusting his bolus dosing to the amount of carbohydrates composing his meals, already using an optimized MDI regimen, and performing regular self-monitoring of blood glucose (at least four controls per day).

3.3.2 **Pump Selection** (Table 3.1)

Insulin pumps have different characteristics: first the type of device including tethered pumps with an external tube connecting the pump to a cannula (Fig. 3.1) or patch pumps with a short tube and cannula integrated into a micro-pump device and controlled by a handled remote control (Fig. 3.2). The former are the most commonly used, and the latter provide the advantage of being smaller and discrete and provide easier set changes and lower risk of tube dysfunction. Patch pumps do not yet offer continuous glucose sensor coupling. Other characteristics of pumps include their size, reservoir volume (1.5–3 ml), battery autonomy, wireless data downloading, ability to link with glucose meters, number of basal rates per day, bolus duration and shape, bolus calculator option, and compatible cannula types.

3.3.3 Pump Programming

Starting pump therapy requires converting the injected insulin doses to pump settings. Fast-acting analogues are the only insulins used in pumps. The total daily dose (TDD) administered by pump derives from that on MDI but is generally reduced by 15–20%. It may be splitted for half into a basal rate (TDD × 0.5), 24 expressed as units per hour (u/h), and for the other half into three meal boluses (TDD × 0.5), 3 (plus snacks if needed). If the baseline HbA1c is high and no hypoglycemia occurred before pump initiation, the TDD should be increased further. Subsequently, the dosing schedule should be refined according to nycthemeral variations in basal insulin requirements: as an example, early morning requirements should be increased due to dawn phenomenon. Such adaptations may result in a basal programing which includes 2–5 different rates per day in average. Bolus administration by pumps may be calculated with the help of a bolus calculator integrated in the device. A bolus may be delivered as a standard bolus (immediate delivery) or alternatively in a square-wave (extended bolus delivered in a defined period of time) or in a multiwave fashion (combo bolus delivered as a combination of immediate bolus and square-wave bolus).

Table 3.1 Characteristics of pump devices

Pump	Medtronic Paradigm Veo 554/754	Medtronic 640 G 1512/1712	Animas Vibe	Roche Accu-Chek Combo	Roche Accu-Chek Insight	Cellnovo PATCH PUMP	Omnipod Insulet PATCH PUMP
Size, mm	51 × 76 × 20	53 × 85/96 × 24	51 × 82 × 22	56 × 82 × 21	52 × 84 × 19	35 × 53 × 14	61 × 41 × 18
Weight, g	103/108	92/96	105	110	122	32	34
Reservoir size, U	180/300	180/300	200	315	160 (prefilled)	150	200
Energy autonomy	4 weeks	3–4 weeks	3–4 weeks	2–3 weeks	10–35 days	Chargeable	3 weeks
Water resistant	Short time, 1 m	24 h, 3.6 m	24 h, 3.6 m	Long time, 2.5 m	1 h, 1.3 m	Short time, 2 m	1 h, 7.6 m
Basal increment, UI/h	0.025	0.025	0.025	0.01	0.01	0.05	0.05
Basal rate number/day	48	48	12	24	24	?	48
Temporary basal	% of current	% of current	−90 to +200%	0–250%	0–250%	?	% or U/h
Bolus increments UI	0.025–1	0.025–1	0.025	0.1–2	0.05–2	?	0.05–1
Bolus types	Stand, extended combined	Stand, extended combined	Stand, extended combined	Stand, extended multiwave	Stand, extended multiwave	?	Stand, extended combined
Bolus calculator	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Max bolus, U	75	75	35	25	25	30	30
On board insulin	Yes	Yes	Yes	No	No	Yes	Yes

(continued)

Table 3.1 (continued)

Pump	Medtronic Paradigm Veo 554/754	Medtronic 640 G 1512/1712	Animas Vibe	Roche Accu-Chek Combo	Roche Accu-Chek Insight	Cellnovo PATCH PUMP	Omnipod Insulet PATCH PUMP
Software download	CareLink	CareLink	Diasend	Smart Pix or 360 diabetes management system	Integrated	Tactile pad	CoPilot Health Management System
CGM integrated	Yes	Yes	Yes	No	No	No	No
Specific functions	Wireless SMBG transfer	Predictive stop SmartGuard	Food database	Handheld combo	Handheld combo	Patch pump integrated SMBG	Patch pump
Catheter type	Silhouette, Quickset, Mio, SureT	Silhouette, Quickset, Mio, SureT	Luer lock system	Luer lock system	Insight	Orbit Integrated	Integrated
Alarms	Sound or Vibracall	Sound or Vibracall	Sound or Vibracall	Sound or Vibracall	Sound or Vibracall	Multiple alarms	?

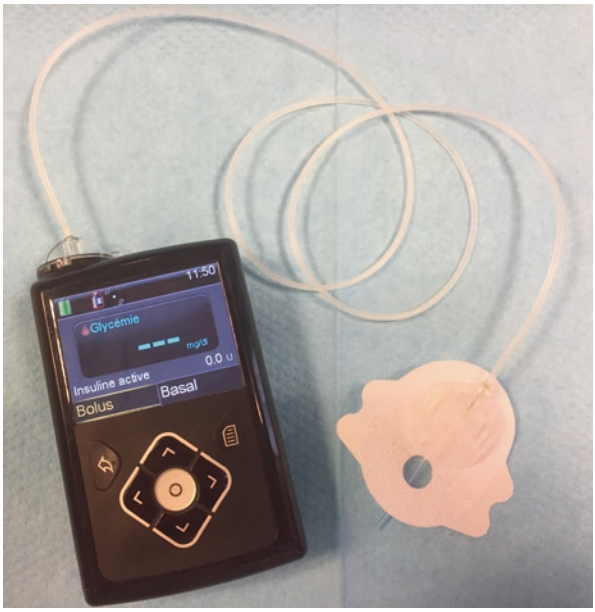

Fig. 3.1 Pump device with its infusion set including tubing cannula and insulin reservoir. Personal picture

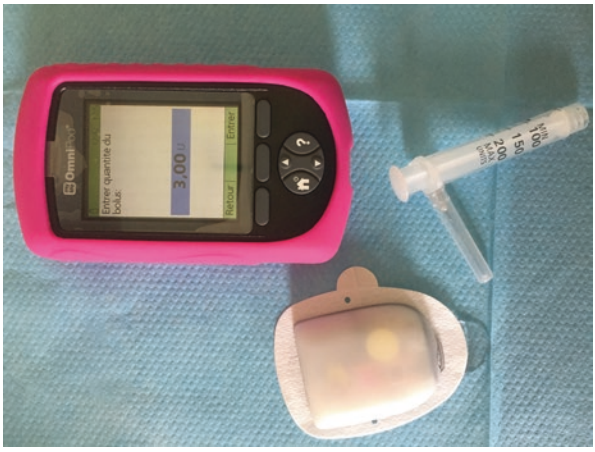

Fig. 3.2 Patch pump. Personal picture

3.3.4 Choice and Management of the Infusion Set and Reservoir

The infusion set is composed of a tubing and a cannula. Tubing length is between 24 and 42 in., its choice depending on the patient's height and the placement of the cannula and the pump during the daytime. The tubing includes a disconnection mechanism allowing to take off the pump for shower, swimming, sports, etc. Cannulas inserted in the subcutaneous tissue have different characteristics: soft flexible cannulas made of Teflon or steel cannulas are easier to insert and less prone to kinking. Angled (20–40°) cannulas are adapted for leaner patients and are less prone to kinking, while perpendicular (90°) cannulas are shorter and are more adapted for arm, hip, or buttock insertion. Cannula length is 6–12 mm for perpendicular cannulas and 17 mm for angled cannulas. Longer cannulas are better for patients with high BMI and high dose requirements.

Pump choice may take account of the reservoir size which depends on daily insulin requirements. A reservoir of 1.5–2 ml fits in most type 1 diabetes pump users, while type 2 pump users will often need a 3 ml reservoir for having sufficient autonomy and avoiding too frequent reservoir filling (Table 3.1). The infusion set may be changed every 3 days to avoid site infection and insulin degradation. The insertion site may be regularly changed with a rotation between the abdomen, thigh, buttock, and arm.

3.3.5 Eating with Pumps

Boluses should be sized to the amount of carbohydrates ingested at each meal. The dose is proposed according to an insulin-to-carbohydrate ratio (ICR) preprogrammed among the 24-h period. ICR may be already determined in previous MDI users and is generally tailored to the breakfast, lunch, and dinner periods. When such ratios are unknown, it may be grossly determined using the "500 rule": dividing 500 by the TDD in units gives the amount of carbohydrates which correspond to a bolus of 1 UI (i.e., if TDD is 40 units insulin, then the ICR will be calculated as 500:40 = 12.5 g consumption needs with 1 unit insulin). For children, the same calculation may be performed with the "300" instead of 500 rule. The bolus dose may also include the amount of insulin corresponding to an eventual fasting hyperglycemia above the glucose target (i.e., if the fasting glucose target is 100 mg/dl, a fasting glucose of 160 mg/dl needs to incorporate the amount of insulin corresponding to a correction of 60 mg/dl). The insulin sensitivity factor (ISF) determined on an individual basis corresponds to the predicted drop of blood glucose evoked by 1 UI insulin. ISF may be determined by the "1800" rule: dividing 1800 by the TDD in units gives the blood glucose drop induced by 1 unit (i.e., if TDD is 40 units insulin, then the ISF will be calculated as 1800:40 = 45 mg/dl blood glucose decrease with 1 unit insulin). After determining these different variables, the ICR, the ISF, and the blood glucose target should be recorded for a daytime period in the bolus calculator, together with the active insulin time which corresponds to

the duration of action of an amount of delivered insulin (3 h is a mean). Then the bolus calculator will be able to calculate the amount of active insulin ("on board" insulin) at any moment of the day. Use of a bolus calculator was demonstrated to reduce postprandial glucose level in pump users randomly assigned to pump with or without bolus calculator [29].

3.3.6 Physical Activity with Pumps

During and after exercise, glucose utilization by muscles and insulin absorption are increased resulting in a risk of hypoglycemia. Therefore, insulin supply by the pump may be reduced together with eventual carbohydrate loading. Practically, the basal rate may be temporarily reduced by 30–50% 1 h before and during the exercise. Alternatively if an exercise bout is planned in the period following meal, the bolus dose prior meal may be reduced by 25–75% of the usual dose. In case of intensive exercise or low-normal blood glucose level before exercise, glucose loading with 20 g of fast-acting carbohydrates may be ingested before and/or during exercise.

3.4 Adverse Events and Caution with Pump Devices

Device-related adverse events are observed in patients wearing pumps including tube breakage, tube or cannula occlusion, leakage at the infusion site, air bubbles inside the tube or reservoir, subcutaneous nodules at the catheter site, skin sensitivity to adhesive, skin infection, and pump malfunctioning. A rate of 36% insulin pump failure was observed in a survey performed by 640 insulin pump users analyzed on a mean period of 15 months [30]. Failure in insulin delivery whatever the cause may increase the risk of diabetic ketoacidosis in pump users. In order to avoid such adverse events, infusion site and tubing should be checked frequently, and infusion site should be changed every 2–3 days respecting site rotation. Skin should be cleaned at each infusion set change. Unexplained high blood glucose should question on a device or infusion set dysfunction.

3.5 Insulin Pumps and CGM

3.5.1 Downloading Pumps

Most pumps allow data to be downloaded. Pump features including basal and bolus insulin amounts, glucose meter data, amounts of ingested carbohydrates, and exercise should be displayed and integrated for global analysis. Smartphone and computer applications are available for uploading pump data and getting periodic advice from healthcare professionals.

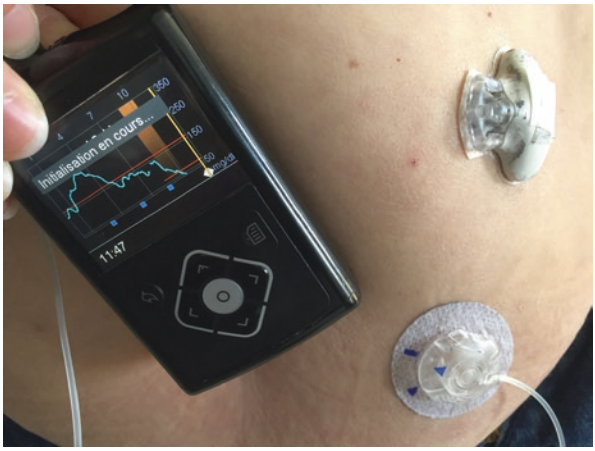

Fig. 3.3 Sensor-augmented pump. Personal picture

3.5.2 Sensor-Augmented Pumps

The importance of frequent self-monitoring blood glucose measurements per day has been largely demonstrated but has limitations including the lack of information on postprandial glucose excursions and of nocturnal hypo- or hyperglycemia. The adjunction of continuous glucose monitoring (CGM) to insulin pump devices allows close monitoring of glycemic variations and helps anticipating hyper- or hypoglycemic events (Fig. 3.3). Sensor-augmented pumps (SAP) have proven to reduce HbA1c by −0.6% in comparison with MDI in a 1-year randomized controlled study [31]. In a 3-month randomized controlled study, the adjunction to SAP of a low-glucose threshold-based insulin pump interruption allowed to reduce nocturnal hypoglycemic events by 31.8% in comparison with SAP without such function [32]. In the most advanced systems, SAP is able to suspend the basal rate when the CGM predicts the future occurrence of hypoglycemia, reducing further the occurrence of hypoglycemia.

3.6 Educational Programs for Insulin Pump Management

Structured education programs are mandatory and may be delivered by multidisciplinary teams. Such programs should include education for pump setting and using basic functions—bolus, basal and temporary basal delivery, suspending basal flow, infusion set management—and more advanced functions, carbohydrate counting and bolus calculator use, square-wave or multiwave bolus, etc., together with behavioral abilities for managing planned or unplanned situations such as hypoglycemia, prolonged hyperglycemia, sick days, intense exercise, travel, stressful situations, etc.

3.7 Cost-Effectiveness of Pump Therapy

Pumps are more expensive than MDI [33], and in some countries, insurance systems should reimburse the additional costs of pump therapy when health economic analysis has proven a significant benefit. The NICE report on cost-effectiveness data for pump therapy performed according to the Centre for Outcomes Research and Evaluation (CORE) diabetes model which integrates the long-term diabetes health and economic outcomes [34]. Several studies have shown a gain in quality-adjusted life-years (QALYs) for type 1 diabetes pump users in comparison with MDI users, such gain being driven mostly by the reduction in HbA1c but also by the reduction in severe hypoglycemic events. A recent multicenter study performed in a parallel-group cluster randomized controlled fashion in 317 patients compared the effectiveness of pump therapy compared to MDI during flexible insulin therapy. Although pump therapy reduced more HbA1c than MDI and increased quality of life related to diabetes, pump was not cost-effective compared to MDI [35, 36]. Cost-effectiveness has been demonstrated in the Netherlands for pump users with type 2 diabetes [37].

3.8 Conclusions

Insulin pump therapy may improve glucose control in a subset of type 1 patients who cannot achieve target HbA1c level despite careful education or at the expense of high rate of hypoglycemia. Pump therapy may also improve glucose control in patients with type 2 diabetes who fail to reach target HbA1c with an intensified basal-bolus regimen using rapid- and long-acting insulin analogues after adequate dose titration. Pump use allows to reduce the rate of severe hypoglycemia in type 1 diabetes patients prone to experiment recurrent episodes. Eligibility for using an insulin pump requires careful patient's selection on his ability to cope with pump device and demands thorough education by skilled professionals. Although more expensive than MDI, pump therapy may prove cost-effective in well-defined indications in type 1 as in type 2 diabetes patients. Coupling sensor technology to pump devices may help reaching glucose control together with limiting further the occurrence of disabling hypoglycemia.

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Continuous Glucose Monitoring Systems

4

Michael Joubert

4.1 Technology and Available Devices

Actually available continuous glucose monitoring (CGM) devices typically consist of (1) a glucose sensor, subcutaneously inserted, that continuously measures interstitial glucose levels; (2) a transmitter connected (physically or wireless) to the sensor; and (3) a receiver displaying glucose data. The technology of these sensors relies on an electrochemical approach using glucose oxidase enzyme (GOx). Sensors are coated with GOx that catalyzes the oxidation of glucose to gluconolactone, producing O_2, H^+, and electrons. Glucose concentration is thus correlated to an electrical signal which is transduced to the transmitter. Then this signal is back translated in glucose values to be displayed on the receiver. Most systems need to be calibrated with regular capillary blood glucose values in order to properly associate glucose values to the electrical signal. Only one system requires no calibration as it is "factory calibrated" (see below). Life span of each sensor type is linked to the subcutaneous stability of GOx and its ability to catalyze glucose oxidation over time. Non-electrochemical technologies are also developed for CGM but are not currently available in routine practice (optical, impedance, piezoelectric, magnetic methods) [1]. CGM data can be displayed in real time to the patient, on a dedicated receiver or directly on the screen of an insulin pump, as a continuous biofeedback. Such CGM systems are called "real-time CGM" (rt-CGM), "therapeutic CGM," or "personal CGM." They are intended to be used continuously, on the long term, to improve metabolic control, thanks to real-time management of diabetes by the patient himself. CGM data can also be recorded during a limited period of time, without being made available to the patient in real time, for retrospective analysis by health-care professionals (HCP), in order to tailor the treatment according to

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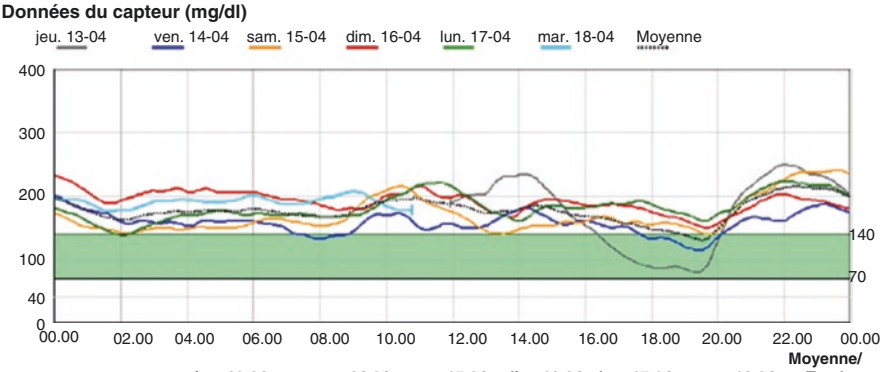
glucose profiles (Fig. 4.1). This use of CGM is named "retrospective CGM" (retro-CGM), "diagnostic CGM," or "professional CGM." It's important to notice that rt-CGM devices, although primarily designed for daily patient's use, also store large amounts of glucose data that can be retrospectively used by HCP to analyze glucose profiles and, thus, can be used as retro-CGM.

The two main types of CGM devices currently on the market are "classic" CGM systems [Enlite® (Medtronic), Dexcom® (Dexcom), Eversense® (Senseonics)], and Flash Glucose Monitoring (FGM), actually represented by the sole FreeStyle Libre® (Abbott).

Enlite® system (Medtronic) refers to the Enlite® sensor and includes rt- and retro-CGM devices. 640G® and 670G® insulin pumps can directly display rt-CGM data on their screen when they are connected to an Enlite® sensor, via a dedicated transmitter.



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Nb valeurs du capteur	145	288	288	288	288	130	1427
La plus elevée	249	201	240	232	223	207	249
La plus basse	80	113	140	150	137	176	80
Moyenne	176	157	169	191	181	191	176
Ecart type	58	17	28	16	21	8	29
% decart Moyen Absolu	2,6	2,6	6,1	1,8	0,7	9,4	3,5
Correlation	N/A	N/A	N/A	N/A	N/A	N/A	0,96
Nb callbrations valides	3	3	4	3	4	2	19
Désignation						x	

X : Faltes appel a votre appreclation dlnique S : Aucune donnee du capteur C : Aucune glyoemle de callbration

Résume dés excursions (mg/dl/jour)

	jeu. 13-04	ven. 14-04	sam. 15-04	dim. 16-04	lun. 17-04	mar. 18-04	Moyenne/ Total
Nb excurslons	2	2	0	1	1	0	6
Nb excurslons hautes	2	2	0	1	1	0	6
Nb excurslons basses	0	0	0	0	0	0	0
AUC superleure a la llmite	48,7	18,8	29,2	51,1	41,5	50,5	37.9
AUC Inferleure a la llmite	0,0	0,0	0,0	0,0	0,0	0,0	0,0

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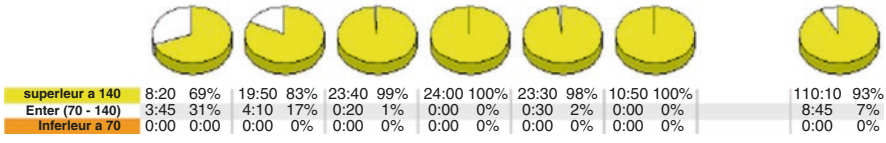

superleur a 140	8:20	69%	19:50	83%	23:40	99%	24:00	100%	23:30	98%	10:50	100%			110:10	93%				
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Inferleur a 70	0:00	0:00	0:00	0%	0:00	0%	0:00	0%	0:00	0%	0:00	0%			0:00	0%				

Fig. 4.1 Example of retro-CGM report. Health-care professional can use this information to tailor diabetes treatment

In addition, these two insulin pumps include hybrid closed-loop systems, with a hypo minimizer and a hypo-hyper minimizer, respectively. These two hybrid closed-loop systems represent the first commercial steps toward artificial pancreas. The Guardian Connect® device allows the user to receive real-time updates from his Enlite® sensor directly on a smartphone app. This system is primarily designed for multiple daily injection (MDI) patients who want to wear a rt-CGM, but inpatients' monitoring could also be an application of this device. iPro2® is a blinded device dedicated to retro-CGM: the system can record CGM data from an Enlite® sensor during its life span of 1 week. Enlite® sensor requires 2–3 calibrations per day (capillary blood glucose), retrospectively filled in the data analysis software with iPro2® system.

Dexcom® (Dexcom) is a sensor that can be connected to rt-CGM devices: a dedicated receiver or a smartphone can be used to display real-time data from this sensor. As Enlite® sensor, Dexcom® sensor has a life span of 1 week and also requires regular calibrations.

Eversense® (Senseonics) is an implantable sensor, inserted subcutaneously on the upper arm, with a life span of 6 months. This system requires an adhesive removable transmitter that is glued to the skin just above the sensor. Real-time glucose data are displayed on a smartphone. In addition, the transmitter may vibrate in case of low glucose value.

FreeStyle Libre® (Abbott) is the sole commercially available sensor of FGM type. This system provides an intermittent access to continuous glucose monitoring. The user can access the last 8-h CGM data by scanning his FreeStyle Libre® sensor with the specific reader or with a compatible smartphone. No calibration by the user is needed with this 14-day sensor, thanks to a factory calibration. However, unlike other sensors, glucose data are not pushed to a receiver, and data access requires an active approach from the user. Thus, FGM does not deliver low and high glucose alarms and is not suitable for patients with hypoglycemia unawareness. FreeStyle Libre Pro® (Abbott) uses the same sensor but with a 14-day memory within the sensor, exclusively designed for retro-CGM. For this device, the reader is just used by health-care professionals to activate the sensor after insertion and to collect glucose data after 14 days of blinded glucose profile recording.

Accuracy of these different sensors has been evaluated by companies in the context of development plans of their devices and by independent academic investigators. Heterogeneous results have been reported. However, accuracy seems to improve over time along with the provision of last-generation sensors. One of the latest independent studies that compared the accuracy of the main three rt-CGM sensors (Enlite®, Dexcom®, and Navigator®(no longer distributed)) found a mean absolute relative difference (MARD) between sensor values and blood glucose of 17.9%, 10.8%, and 12.3%, respectively, for more than 4500 paired values for each system. Sub-analysis of accuracy in different blood glucose intervals revealed that Dexcom® and Navigator® outperformed Enlite® except for blood glucose values above 250 mg/dL, where Dexcom® outperformed two others. The Clarke error grid approach, used to assess the clinical significance of differences between sensor glucose and blood glucose reference measurements, showed that 69.1%/84.5%/84.2% values were in zone A, 29.8%/15.1%/14.2% in zone B, 0.3%/0%/0% in zone C, and

0.8%/0.5%/1.6% in zone D, for Enlite®/Dexcom®/Navigator® sensors, respectively [2]. Recently, FreeStyle Libre® accuracy has also been evaluated and compared to Dexcom® sensor, considered actually as the gold standard sensor. Average glucose profiles and MARD versus SMBG were similar between these two sensors. Time spent in normo-, hyper-, or hypoglycemia and indexes of glucose variability were also similarly estimated by the two sensors [3]. Accuracy of Eversense® implantable sensor is announced by the developing team as the best accuracy of the market with a MARD of 8.8% and 99.3% values in zones A and B of the Clarke error grid [4].

4.2 Retrospective CGM

The theoretical value of retro-CGM is clear, as it allows the identification of glucose patterns and of previously unknown hypo- or hyperglycemic drifts, especially during periods poorly explored by SMBG such as nighttime and postprandial periods. It has been previously demonstrated that the use of retro-CGM increases detection of hyperglycemic episodes in both children and adults compared with SMBG [5–8]. Several studies have shown that retro-CGM may also reveal hypoglycemic episodes especially at night, reaching an incidence of 70% and a time duration of 20% in some studies [5, 6, 8–12]. In addition, through adaptation of insulin regimen, retro-CGM can reduce the incidence of hypoglycemic episodes in both type 1 and type 2 diabetic patients [9, 13]. Results of CGM on HbA1c are more conflicting, with two pediatric trials showing significant HbA1c improvement of −0.3% to −0.4% with regular use of retro-CGM [14, 15] and other reports finding no superiority of such devices compared with SMBG [13, 16–18]. Other studies have also highlighted the value of retro-CGM for flexible insulin therapy education, during pregnancy or in challenging diabetes situations like dialysis [19–21]. To contextualize glucose profiles and facilitate a complete, comprehensive interpretation, CGM recording analysis requires additional clinical information, such as the patient's life situation, treatments, carbohydrate intake, and management of diabetes. These data should ideally be provided and collected by caregivers and the patients themselves throughout the CGM recording. When removing the CGM device, the health-care professional should check that the relevant data have been collected and fill in any missing information with the help of the patient and his glucose meter if necessary. Retrospective analysis of CGM profiles requires a step-by-step approach: (1) data quality evaluation, (2) overall profile analysis, and (3) day-by-day profile analysis [22]. This last step is of paramount importance when overall profile analysis reveals huge inter-day variability, making it difficult to give patient general advices. Day-by-day profile analysis is more valuable when done concomitantly with the patient, allowing to have all context information and to engage the patient in an educational process. Recently, a medico-economic evaluation suggested that the use of repeated retrospective CGM in patients with type 2 diabetes could be cost-effective, thanks to targeted therapeutic adjustments [23]. In the near future, CGM profiles may probably be integrated in therapeutic guidelines for type 2 diabetes management, as part of the parameters to be taken into account before choosing a therapeutic strategy.

4.3 Real-Time CGM

Whereas retro-CGM can provide interesting information in patients with any type of diabetes and any type of treatment, rt-CGM is mainly dedicated to T1D patients treated by intensive insulin therapy. Indeed, the concept of rt-CGM is to offer a real-time glucose feedback to facilitate daily self-management of diabetes. Thus, most studies assessing rt-CGM involved T1D patients and demonstrated a 0.3% decrease of HbA1c in T1D patients using rt-CGM for 3–6 months. This HbA1c improvement ranged from −0.2% to −0.9%, according to baseline HbA1c and to sensor adherence (greater A1c improvement in patients with higher baseline HbA1c and higher adherence to the sensor) [24]. Besides HbA1c improvement, rt-CGM can also reduce the hypoglycemic risk as it was showed in T1D patients with baseline well-controlled HbA1c: the use of rt-CGM reduced the time spent in hypoglycemia of about 50%, both with "classic" CGM and FGM [25, 26]. For patients with hypoglycemia unawareness, "classic" CGM remains more efficient to reduce hypoglycemic episodes, compared to FGM that does not provide alerts in case of low glucose values, especially during night periods [27]. Historical studies exploring rt-CGM majorly involved insulin pump users as it was considered, until recently, that this treatment modality was preferable to achieve the therapeutic real-time adjustments suggested by CGM. However, three recent trials demonstrated that rt-CGM was also effective in multiple daily injection (MDI) patients. First, the DIAMOND study explored 158 T1D MDI patients that were randomized to rt-CGM or usual self-monitoring of blood glucose (SMBG). After 6 months, rt-CGM patients displayed a 0.6% decrease of HbA1c compared to SMBG patients [28]. The GOLD study, with a similar method, also showed a 0.4% HbA1c decrease, thanks to rt-CGM [29]. The IMPACT study also highlighted the interest of rt-CGM in MDI patients. In this study, where 70% T1D patients were on MDI, the use of FreeStyle Libre® (flash glucose monitoring system) for 6 months resulted in a 40% decrease of time spent below 70 mg/dL, both during daytime and nighttime. In addition, time spent above target was also decreased, resulting in an overall stable HbA1c, while the glucose profile was obviously improved, with an increased time in range [26]. There is paucity of data regarding the effect of rt-CGM in T2D patients. However, a randomized study reported that the intermittent use of rt-CGM for 12 weeks in T2D patients who were not on prandial insulin resulted in a 0.5% decrease of HbA1c compared to SMBG patients. This HbA1c decrease was sustained over 40 weeks, despite the use of rt-CGM only during the first 12 weeks, suggesting the educational role of rt-CGM in this population. Furthermore, although the burden of diabetes medications increased in both groups during this study, there was no difference between the groups in the number of medications at the end of the follow-up, suggesting that lifestyle modifications prevailed [30]. The REPLACE study explored the effect of FGM technology for T2D patients: authors failed to demonstrate HbA1c reduction, but the use of FGM significantly reduced of approximately 50% the hypoglycemic events at 6 months [31].

4.4 New Glucose Metrics

Increasing use of CGM, whether retrospective or in real time, leads to the emergence of new glucose metrics, thanks to the large amount of glucose data generated by CGM devices. HbA1c has remained the main glycemic control assessment for many years since it was demonstrated that this parameter correlates with long-term complications. HbA1c is also the gold standard in all diabetes treatment guidelines, with recommendations of treatment adaptations when HbA1c is above a personalized threshold. However, large intervention studies (like the ACCORD study) have demonstrated that too low HbA1c are not associated with reduced cardiovascular events and can even be a marker of frailty and be associated with increased mortality. The relation between HbA1c and all-cause mortality has been shown to be J-shaped, with increased events for HbA1c above 8% and below 6% [32]. This relation highlights that HbA1c does not only reflect hyperglycemia exposure but also hypoglycemic episodes, averaging all hyper- and hypoglycemic drifts. In addition, HbA1c does not report glycemic variability that may yet be dramatically different between two patients with the same A1c values. Limitation of HbA1c to portray glucose control and profile is now taken into account by researchers: in recent clinical trials, already published or actually ongoing and recorded in public registry, composite evaluation criteria are increasingly used, combining HbA1c with other parameters like hypoglycemia occurrence and/or body weight change [33]. Furthermore, CGM metrics are more and more often used as primary end point in many diabetes clinical trials. CGM data offer a global picture of glucose control with objective assessment of hyperglycemia exposure, hypoglycemic episodes (deepness and duration), glucose variability, and also time in range (TIR) (i.e., time spent within normal range of glucose) which is the ultimate goal of diabetes treatment. In addition to these statistic values, CGM data analysis software also offers a graphical representation of the glucose profile. The ambulatory glucose profile (AGP) is a presentation of CGM data, developed by an academic team, independent of proprietary software, and clearly outlining all the information that one can expect from a CGM [34]. Artificial pancreas devices are naturally assessed by CGM metrics as the aim of these closed-loop systems is to maintain glucose values within normal range. The CGM outcomes mandatory in closed-loop development were consensually defined in 2016 [35]. Beyond their use for closed-loop systems, such CGM metrics are able to report both efficacy (increased TIR, decreased hyperglycemia exposure) and safety (not increased hypoglycemia exposure) of any diabetes treatment. In daily routine practice, the use of CGM metrics may help counteract clinical inertia as therapeutic decisions can result from the CGM data analysis, without waiting the 3 months that is necessary to observe HbA1c changes. In addition, most CGM analysis software includes an estimated HbA1c which is calculated from CGM data, allowing to extrapolate the midterm glucose control based on short-term glucose data (Fig. 4.2). Two recent international guidelines have specified the CGM metrics to be evaluated in clinical practice, with a clear definition of the thresholds for normal, high, and low glucose range [36, 37].

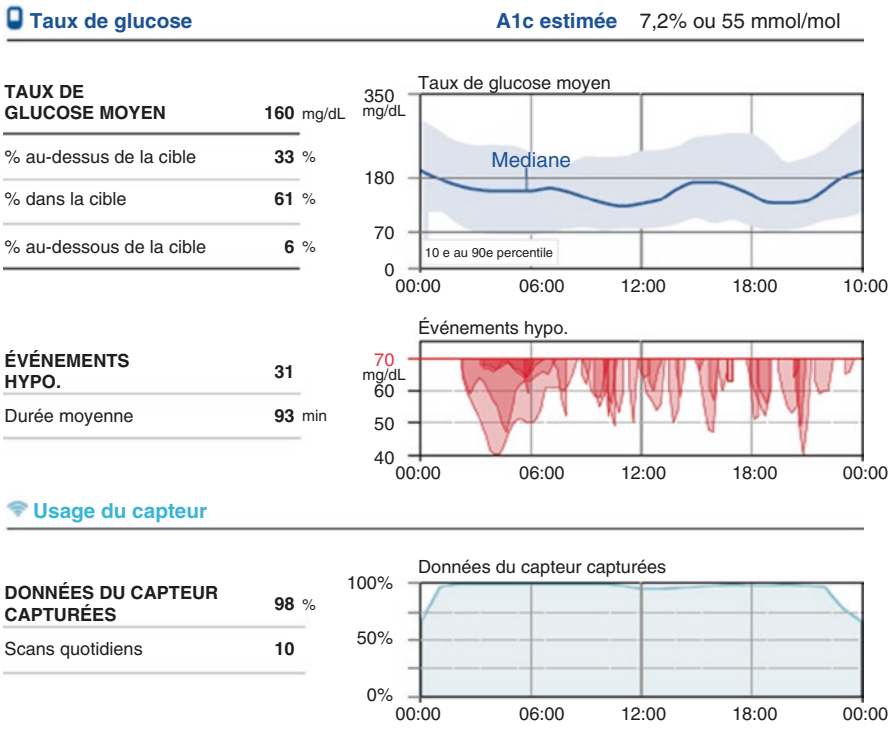

Fig. 4.2 CGM report including estimated HbA1c calculation

However, additional issues need to be addressed before CGM metrics will completely replace HbA1c: Is TIR an acceptable long-term surrogate end point to manage diabetes? Does TIR correlate with long-term complications? How to use TIR to guide therapeutic strategy while recommendations are based on HbA1c? What is the expected TIR value in a patient with well-controlled diabetes?

These questions will need further studies to be addressed but the history of CGM is on, and it seems likely that it will supplant both the capillary blood glucose self-monitoring and HbA1c in the upcoming years.

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The Implantable Insulin Pump

5

Pauline Schaepelynck

The implantable insulin pump is a treatment option for certain patients with type 1 diabetes when an external insulin pump has failed to stabilize their diabetes despite all appropriate medical and educational efforts. The implanted pump provides an added efficacy for glycemic variability, hypoglycemia, and HbA1c as compared to the external pump's subcutaneous insulin delivery. This is due to the intraperitoneal insulin administration which is now shown to have long-term and sustainable metabolic benefits. Insulin treatment using an implanted pump is a result of over 30 years of progress in technology and insulin preparation.

5.1 Properties of the Intraperitoneal Administration of Insulin

The implantable pump's main interest lies in the intraperitoneal delivery of insulin, which is more physiological and reactive than a subcutaneous delivery. Insulin delivered directly into the abdominal cavity is picked up by the liver via the portal system. This insulinization of the liver makes it possible to restore more physiological gradient insulin between the portal and peripheral circulation as compared to a subcutaneous route [1]. In comparison with subcutaneous (SC) delivery, intraperitoneal (IP) delivery enables faster insulin absorption with an earlier and narrower insulin peak level after the bolus, as well as a quicker return to the base value [2]. Additionally, the IP route is more responsive to changes in pump rates with a better replication from 1 day to the other [3] (Fig. 5.1). It has been shown that with IP insulin delivery, there is a partial restoration of the glucagon response to

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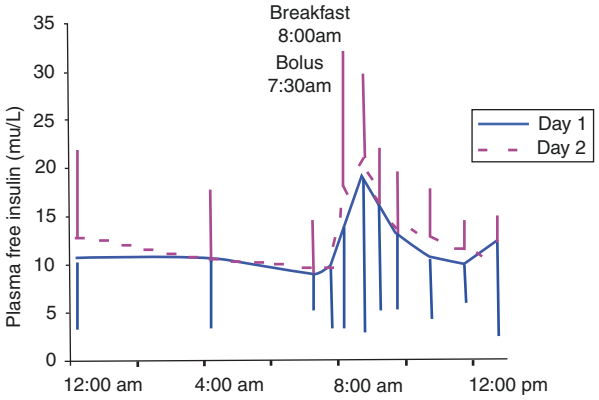

Fig. 5.1 Plasma-free insulin profiles (m ± SD) on Day 1 and Day 2 with implanted insulin pump [3]

hypoglycemia [4]. These characteristics of the IP route explain the long-lasting metabolic benefits already reported in many studies with implanted insulin pump [5–11] such as reduced severe hypoglycemia, less glycemic variability, and a better control of diabetes than with an intensified SC insulin therapy.

Moreover, the intraperitoneal insulin therapy's improved portal insulinization prompts other beneficial effects beyond blood glucose. These include the effects on the GH/IGF1 system (increased IGF1 hepatic production and of its serum bioactivity [12, 13]), as well as favorable effects on metabolism and on hepatic oxidative stress and inflammation which have been demonstrated on diabetic rats [14].

5.2 The Current Implantable Insulin Pump

The only model currently available is the MIP 2007D, marketed by Medtronic® (Photo 5.1). The pump, whose case is made of titanium, is surgically implanted into the abdominal wall (Photo 5.2), and the catheter's distal end is introduced into the peritoneal cavity with a small fascial incision through the abdominal muscles and peritoneal layers. The procedure is performed under general or local anesthesia. The pump has approximately an 8-year life and is programmed by radio frequency with the "PPC" (personal pump communicator).

Percutaneous refills of the insulin reservoir are done every 6 weeks under strict aseptic conditions. The refill takes about 20 min. The pump infusion accuracy is evaluated at each refill by calculating the pump percentage of error corresponding to the ratio between the amount of insulin actually delivered by the pump and the theoretical volume programmed (calculated by the PPC) since the previous refill. A percentage of error greater than 15% is considered significant and reflects an under-delivery of insulin. Systematically rinsing the pump every 6–9 months with a 0.1 N sodium hydroxide solution is recommended to prevent insulin aggregates forming in the pump's mechanism. Additional rinsing can be achieved, with or without a catheter "flush" in case of an insulin under-delivery when there is a suspicion of

Photo 5.1 The current implantable insulin pump (MIP 2007D, marketed by Medtronic). Source: www.evadiac.org

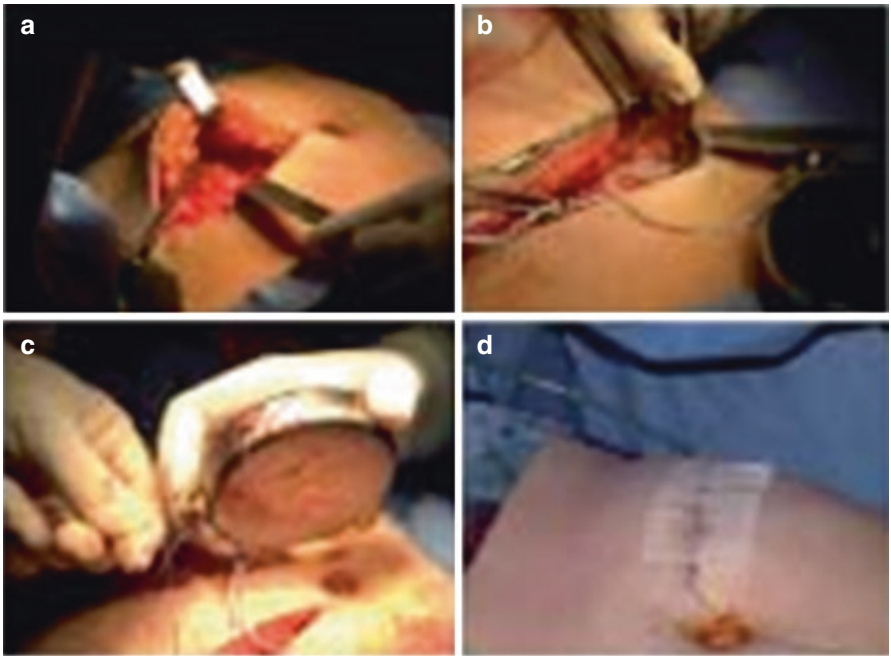

Photo 5.2 Surgical implantation of the pump into the abdominal wall. Pump implantation procedure: (**a**) creation of the subcutaneous pocket for the pump implntation (**b**) insertion of the distal part of the catheter in the peritoneal cavity (**c**) pump fixation (**d**) closing by cutaneous suture. From Hanaire et al., Revue Médecine des Maladies Métaboliques, vol 6, nb 6, décember 2012

deposits in the reservoir and/or a catheter obstruction. Rinsing is an outpatient procedure which in most cases lasts 30–60 min.

5.3 The Implanted Pump's Evolving Role in Diabetes Management

5.3.1 The First Insulin Pump Implantations in Humans

The first implantation occurred in 1980 in the United States on a type 2 diabetic patient with an Infusaid® pump to intravenously deliver insulin via a single

pulsatile flow [15]. The pump was implanted in the clavicular cavity, and the catheter was inserted into the superior vena cava via the cephalic vein. Then the first tests with the PIMS (Programmable Implantable Medication System) by MiniMed® were performed in 1986. This insulin pump, the precursor of the current Medtronic MiniMed® pump, had a variable flow and an intraperitoneal delivery [16].

5.3.2 The Stability of Insulin Used: A Determinant of Good Pump Function

By the 1980s, insulin's stability in implanted pumps was recognized as a major prerequisite [17] since it is a fragile protein, which tends to precipitate and form aggregates as well as become denatured. In order to be used with an implanted pump, the insulin solution must logically meet the criteria of biological and chemical stability, physical stability, and compatibility with the components of the pump. The obstacles are many: prolonged stasis in the pump reservoir between filling cycles, exposure to body temperature and mechanical stress associated with pulsatile movements of the piston, contacts with hydrophilic surfaces and metal (titanium), etc. There were several insulin preparations specially formulated for implanted pumps and tested in vitro and in vivo, but clinical experience with implanted pumps really began with the development of a semisynthetic human insulin preparation, insulin HOE 21PH (Hoechst [later Aventis Pharma], Frankfurt, Germany). This insulin, concentrated to 100 or 400 U/mL and stabilized with poloxamer 171 (polyethylene-polypropylene glycol) to inhibit aggregation, had a clinically validated 1–3-month stability and compatibility with the reservoir fill cycles.

5.3.3 France's Experience with the Creation of the EVADIAC

The first implantations appeared in France in 1989, and the EVADIAC group (Evaluation of Active Implants in Diabetes) was created in 1990, thus uniting all the French pump implantation centers with a primary mission of vigilance of this therapeutic modality. The early 1990s saw the implanted pump's use spread in France with three pump models: Infusaid®, MiniMed®, and Siemens®. In 1994 a significant number of catheter obstructions and pump slowdowns occurred due to an insulin stability defect in the reservoirs and catheters. As a result, two of the firms withdrew from production, and only MiniMed® continued to make hardware improvements (such as a catheter with anti-backflow valves and side port able to purge obstructions, etc.). Technical procedures and insulin's stability continued to improve, and in 1998, the insulin preparation HOE 21PH obtained market authorization under the name Insuplant® 400 IU/mL (Aventis Pharma, Frankfurt am Main, Germany). The technique underwent a new impetus with the MiniMed® pump, MIP 2001 (MiniMed®

Implantable Pump), receiving approval in France along with EVADIAC group's publication of good practice rules [18].

In early 2000, MiniMed® rejoined Medtronic and subsequently produced the MIP model 2007 with an operating period extended from 3 to 8 years. Each evolution of the MIP 2007 pump has received a CE marking (declaration of conformity), and beginning in 2008, the implanted pump has been reimbursed by health insurances when used as a replacement to pre-existing pumps. In early 2016, reimbursement has been obtained for a limited number of pumps for new patients.

5.3.4 A Recent Development: Marketing Authorization for a New Insulin Preparation for Implanted Pumps

HOE 21PH insulin or Insuplant® was used until July 2011 when it was replaced by a new insulin preparation, the Insuman® Implantable 400 IU/mL (Aventis Pharma, Frankfurt am Main, Germany), a human recombinant insulin specifically designed for the implantable pump. Both Insuplant and Insuman were compared in a randomized clinical trial [19]. The study was conducted for four filling cycles after which the non-inferiority of Insuman compared to Insuplant was demonstrated on the criteria for efficiency and safety, namely, the HbA1c and pump infusion accuracy. Furthermore, during the study, insulin doses and incidence of metabolic and technical side effects did not differ between each group. The study shows Insuman to be effective and reliable with the implantable pump. Afterward Insuman® received the European marketing authorization in September 2013.

In 2016 Insuman began to be distributed in specialized diabetology centers as required by the European Medicines Agency (EMA). The EMA approval states that "Insuman Implantable is intended for the treatment of type 1 diabetes mellitus that cannot be controlled with subcutaneous insulin (including pump) therapy, presenting with frequent, otherwise unexplained severe hyper- and/or hypo-glycaemia."

5.4 Efficiency and Safety: Published Clinical Evidence

A review of the literature [20] provided an update on the clinical evidence for the efficacy and safety of the implanted insulin pumps using HbA1c, hypoglycemia, and complications of therapy criteria. In 94 randomized or observational studies published, 15 papers on implanted pumps were selected reporting on 4 randomized studies and 8 cohort studies. The study selection took into account the overlap of populations since most patients in the randomized studies were also later included in the cohort studies. Study results showed that in the medium and long term, levels of HbA1c (Fig. 5.2) and hypoglycemia were reduced with the implanted insulin pump. The implanted pump's superiority is particularly apparent in a subgroup of patients who failed to achieve satisfactory glucose control with an external pump.

Additionally glycemic variability is significantly reduced with the implanted insulin pump compared to subcutaneous insulin treatment. This is true whether

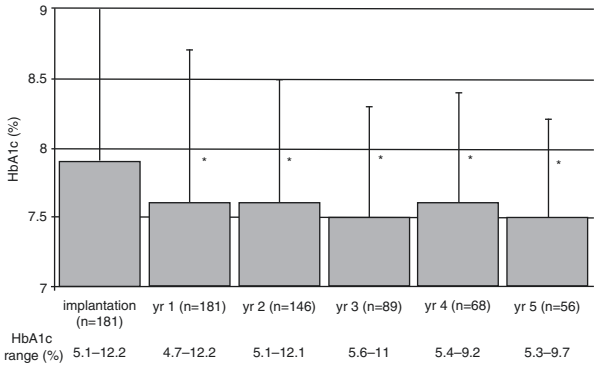

Fig. 5.2 Evolution of mean (±SD) HbA1c values over the years of implanted pump therapy in type 1 diabetic patients, $^{*}p < 0.05$ versus baseline [10]

expressed by standard deviation of the mean capillary blood glucose [8, 21, 22] or by the coefficient of variation of data from continuous glucose monitoring [23].

Moreover, a Dutch study observed a decrease in the duration of hospital stays for implanted insulin pump patients as compared to hospital stays prior to having an implanted pump [24].

The implanted pump has a favorable benefit-to-complication ratio and high patient satisfaction [25]. Complications and their frequencies vary between studies and over the time. These include pump slowdowns linked either to the formation of insulin aggregates or catheter obstruction, skin problems at the implantation site, pump failures, or surgical reprises. In an observational study that monitored 580 cumulative patient-years [10], the EVADIAC group reported an incidence of complications leading to a temporary removal of the pump due to electronic pump failure for 0.5/100 pt-yr, catheter obstructions for 0.86/100 pt-yr, blocked pumps for 1.2/100 pt-yr, pump pocket infections for 1.4/100 pt-yr, or premature battery depletion life for 2.24/100 pts-yr. These complications are usually remediable, though some cases require another surgery.

Elevated anti-insulin antibody levels were observed in 40–76% of patients with implanted insulin pump. Of these patients, 8–36% experienced late night hypoglycemia [26–28].

5.5 Current Situation and Perspectives of Implantable Pump

Although the insulin implantable pump is not a first-line treatment, it is still regrettable that it has limited accessibility to those that could benefit from its potential to stabilize their diabetes. The implantable pump is not available outside Europe and is no longer available in the United States. It is currently accessible to a limited number of patients and diabetes centers in France, Belgium, Sweden, and the Netherlands [29]. In 2017, approximately 400 patients were treated with an

implanted pump, which included 315 patients within the 12 EVADIAC centers in France. The reasons for this limited access are multiple: production costs, limited materials, reimbursement which was previously restricted to replacement pumps, requirement of qualified centers, and, more recently, certification conditions established by the EMA for marketing Insuman.

Recent developments in marketing implantable Insuman insulin and in reimbursement of primo implantations had offered an optimistic outlook for the distribution to new patients in established and new centers in France and Europe. Unfortunately in 2017, Medtronic announced that it was ceasing the production of the implantable insulin pump and was looking for a buyer. Actually the only implantable pump model currently available is technically outdated, and new technologies need to be done which might include a reduction in size, advanced features, and even a coupling with a continuous (intraperitoneal) glucose monitoring system. Besides, a renewed interest for the IP route is emerging since artificial pancreas studies show the superiority of IP insulin delivery over SC delivery for glycemic regulation [30].

All in all, the implanted insulin pump is clearly a therapeutic option for some diabetic patients who fail to achieve stable metabolic control with intensified subcutaneous insulin therapy. This method has been demonstrated as safe and effective in specific situations such as type 1 diabetic patients experiencing a high glycemic variability due to the persistence of unexplained hypo- and/or frequent hyperglycemic events or those whose glycemic control remains poor despite intensified SC insulin therapy and in patients with documented disorders of subcutaneous insulin absorption. This outpatient procedure is much more accessible and easier to achieve than we imagined, and the delivery and means are within the reach of many more diabetes centers than the 12 EVADIAC centers currently operating.

Recent advances with the coupling of “insulin and pump” and regulatory and commercial aspects could allow us to envision reaching an expanded patient population on condition that technological improvement regarding the implantable insulin pump can be funded and completed.

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Closed-Loop Systems

6

Eric Renard

6.1 Early Steps of Closed-Loop Systems

Loss of insulin secretion in type 1 diabetes (T1D) implies the vital need of insulin administration which became available shortly after the discovery of insulin in 1921. However the variability of body insulin needs due to the many factors which influence blood glucose levels results in a difficult task for matching timely delivery of insulin according to T1D patient's need. In order to allow fast tuning of insulin delivery, continuous infusion modulated according to blood glucose levels is needed. For fulfilling these objectives, bedside artificial (endocrine) pancreas models have been developed in the 1970s, almost simultaneously in Europe, Japan and Northern America [1–3]. These systems, such as the Biostator® [4], included intravenous (IV) insulin infusion from a motor-driven syringe, continuous glucose measurement (CGM) by an extracorporeal enzymatic sensor from an access to IV blood and a computing system that drove insulin delivery to keep glucose levels in a close to normal range based upon proportional-derivative (PD) algorithms. These feedback algorithms modulate insulin delivery according to the difference between the current glucose level and the target level (proportional component) and the glucose rate of change (derivative component). An IV glucose infusion line was also available in case of glucose lowering toward hypoglycaemia. These systems were shown to be able to keep blood glucose in a near-normal glucose range. The technologies were however unavailable by these times to allow ambulatory implementation.

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While portable insulin pumps were gradually developed from the 1980s, mostly using subcutaneous (SC) insulin infusion, the lack of reliable glucose sensors allowing wearable CGM remained the bottleneck for further progression toward an outpatient use of artificial pancreas (AP).

From 1993, the results of the Diabetes Control and Complications Trial documented the need for targeting near-normal glucose restoration in patients with T1D in order to prevent diabetes complications [5]. The availability of sufficiently safe and accurate SC glucose sensors from 1999 thanks to MiniMed Technologies research and developments opened the door for a renewal of the AP concept for diabetes care [6]. Meanwhile, modelling of glucose metabolism and insulin action led to the development of simulation platforms that allowed the design and the assessment of closed-loop algorithms through in silico trials in which virtual patients with diabetes could be submitted to insulin infusion according to glucose evolution [7]. Attempts were initially performed to develop and investigate in patients with diabetes sophisticated fully implanted closed-loop systems which combined IV glucose sensing via implanted long-term sensors placed through jugular or subclavian access and intraperitoneal (IP) insulin delivery from implanted pumps [8]. The rationale for this initial choice was based upon the expected fast glucose sensing and insulin action thanks to the respective IV and IP routes. Using PD algorithms derived from earlier experiments with bedside AP systems, or secondarily newly designed proportional-integral-derivative (PID) algorithms to take into account the observed internal delays of glucose sensing inherent to the implanted sensors and the somewhat delayed insulin action of IP insulin compared to IV insulin, closed-loop glucose control could be reported in 48-h hospital trials with up to 91.7% time spent in 80–240 mg/dl glucose range [9]. The invasiveness and limited lifetime of implanted IV sensors led to a move to SC sensors connected to IP insulin pumps which allowed keeping glucose in 80–180 mg/dl range for 76.5% of time in hospital trials under a hybrid closed-loop design including priming premeal bolus [10]. Nevertheless, the limited extension of IP insulin use worldwide compared to the broadly adopted continuous subcutaneous insulin infusion (CSII) from wearable pumps drove the research efforts toward the privileged SC sensing-SC infusion combination, supported by funding from the Juvenile Diabetes Research Foundation (JDRF) from 2006, US National Institutes of Health (NIH) from 2009 and European Union (EU) from 2010.

While ADICOL experience [11] with simulated SC glucose sensing and newly designed model predictive control (MPC) algorithms which took into account delays of SC sensing and SC insulin action had shown the feasibility of a semi-closed-loop insulin delivery (i.e. closed-loop control between meals and prandial insulin bolus), the first full closed-loop 30-h inpatient clinical experiment with actual SC sensing, SC insulin infusion and a PID algorithm was reported by Steil et al. in a landmark paper in 2006 [12]. Glucose was kept for 75% of time in 70–180 mg/dl range which was significantly higher than 63% of time when the patients managed their insulin pumps by themselves for 3 days as outpatients. However, time spent below 60 mg/dl was not reduced under closed-loop glucose control. Indeed, full closed-loop insulin delivery at meal times resulted in early

blood glucose spikes followed by late post-meal hypoglycaemia due to the delayed action of SC infused insulin in response to the increase of blood glucose levels following meal intakes. This phenomenon could be prevented by manually ordered premeal bolus as shown by Weinzimer et al. [13]. Hence, further developments of AP systems using SC glucose sensing and SC insulin infusion have followed this hybrid configuration of closed-loop, also called semi-closed-loop, which includes meal announcement so that meal intakes are preceded by an insulin bolus computed according to the carbohydrate component of the meal, the premeal blood glucose level and the estimated 'insulin on board' according to insulin infusion rate [14].

6.2 Development of Hybrid Closed-Loop Systems with a Primary Goal of Safety

Following the first trials that showed the feasibility of closed-loop insulin delivery by SC glucose sensing and SC insulin delivery, the primary concern became the prevention of hypoglycaemia while using these systems since a failure on this matter would prevent any progression toward outpatient use of AP. Because nocturnal hypoglycaemia is especially fearful in young T1D patients, Hovorka et al. assessed for the first time in children and adolescents how an AP system using an MPC algorithm could reduce the risk of hypoglycaemia at night while improving time spent in a near-normal glucose range compared to CSII [15]. In their seminal paper which cumulated three randomized control trials, these authors reported in a pooled analysis an increase of percent time spent in the target range (70–145 mg/dl) from 40% to 60%, while percent time spent below 70 mg/dl was reduced by half from 4.1% to 2.1%. Similar results were reported by Kovatchev et al. in adult T1D patients who were investigated for night-time control in three different clinical research centres in the United States, France and Italy using another combination of SC glucose monitoring system, SC insulin pump and MPC algorithm, although not in randomized order: percent time in target range (70–140 mg/dl) increased from 64% to 78%, while cumulated hypoglycaemic events below 70 mg/dl were reduced from 23 to 5 in the 20 investigated patients [16].

Meanwhile, the Boston University group assessed the feasibility of an AP system which combined SC glucose monitoring and both SC insulin and SC glucagon infusions, driven by an MPC algorithm and a PD algorithm, respectively [17]. While glucose was kept for 68% of time in 70–180 mg/dl target range with minimal time spent in hypoglycaemia (0.7%) during 51 h, the percent time in target overnight reached 93%. These results suggested a potential additional benefit of glucagon infusion for minimizing hypoglycaemia at the cost of a more cumbersome system due to the need of wearing two infusion pumps and changing glucagon solution daily because of its poor physical stability.

In order to further reduce the risk of hypoglycaemia while keeping single-hormone (insulin) infusion, the concept of a safety supervising module working in addition to the range control algorithm was brought by the international AP

(iAP) study group gathering the University of Virginia; the University of California, Santa Barbara; the Universities of Padova and Pavia; and the University of Montpellier [18]. This modular control-to-range algorithm was assessed during 22-h admissions in two randomized control studies versus CSII, showing its ability to keep glucose between 70 and 180 mg/dl for 97% of time and between 80 and 140 mg/dl for 77% of time with a reduction by 2.7-fold of time spent below 70 mg/dl and reduced overnight glucose variability [19]. Moreover, these investigations reported for the first time the ability of closed-loop control to reduce significantly mean blood glucose level without increasing hypoglycaemia in hospital setting.

The safety of closed-loop systems for glucose control at night-time was further confirmed by the DREAM group which gathered childcare teams of Tel Aviv, Hannover and Ljubljana. This consortium used an MD-Logic algorithm based on fuzzy logic design, i.e. on the estimated risks of hyper- or hypoglycaemia according to physician and patient experiences without any pre-established equations linking glucose level to insulin delivery [20]. This algorithm was run on a laptop which received inputs from continuous SC glucose sensing and sent outputs to a SC insulin infusion pump. Children hosted in diabetes camps showed reduced occurrence of hypoglycaemic events and time spent in hypoglycaemia overnight when using the AP system compared to CSII during two nights submitted to each option in randomized order.

Besides extending the study period over 24 h, the EU-funded 'AP at home' consortium randomly assessed in 48 adult T1D patients two MPC algorithms (one from the University of Cambridge and one from the iAP study group) compared to patient use of a sensor-augmented pump (SAP) about their ability to keep blood glucose in 70–180 mg/dl range [21]. While time in target range was similar with the two AP options and SAP (close to 60% over 24 h), the AP systems appeared as safer since percent time spent with blood glucose below 70 mg/dl was 2% and 2.1% vs. 6.4% with SAP. From this demonstrated and confirmed safety of the various closed-loop systems, a move to experiments in a less controlled environment was considered. These so-called transitional trials aimed at demonstrating the feasibility, the safety and the efficacy of closed-loop systems in home-like conditions. A key element of feasibility was the availability of a wearable platform able to run the control algorithm and to offer an easy-to-understand interface to the patient so that he/she could monitor AP functioning.

6.3 Assessment of Closed-Loop Systems in Home-Like Setting

Following the DREAM study mentioned above, several studies have been performed in diabetes camps, mostly in children and adolescents with T1D, in recent years in the United States in order to assess the safety and the efficacy of closed-loop systems while the patients were hosted in a less protected environment than in a Clinical Research Centre. Closed-loop was active either overnight only or day

and night during periods of 5–6 days. Systems with insulin use only showed similar percent time in target range under closed-loop vs. SAP overnight [22] or vs. SAP with threshold low-glucose suspend during day and night [23]. A bi-hormonal system (insulin and glucagon) showed lower mean sensor glucose and percent time with glucose below 60 or 70 mg/dl when compared to patient use of an insulin pump [24].

If one considers that a diabetes camp does not really mimic home setting, the first report of 'true' outpatient AP use was published by the Universities of Montpellier and Padova after a patient at each site had spent 28 h in near free-life conditions (sleeping in a hotel, taking meals in restaurants, walking in town, etc.) with glucose control obtained from a wearable closed-loop system in which CGM device and insulin pump were connected to the Diabetes Assistant (DiAs) device, based on a smartphone hosting a patient interface and running an MPC algorithm [25] (Fig. 6.1). The patient interface allowed the patient to know at all times sensor-measured glucose, rate of insulin delivery and estimated risks of hypo- or hyperglycaemia through two 'traffic light' icons. Green lights meant no significant risk, whereas a yellow light informed the patient of an identified risk of glucose deviation that the system was able to manage, and a red light requested

Fig. 6.1 First prototype of wearable artificial pancreas system used in home-like setting by patients with type 1 diabetes. Subcutaneous insulin infusion is delivered by an OmniPod (Insulet, Boston, USA) wirelessly connected to a handheld relay ('green box') which receives glucose sensor signal (Seven Plus, Dexcom, San Diego) from CGM transmitter (lower left hand side device) and transmits by Bluetooth the glucose signal to the smartphone-based Diabetes Assistant (DiAs, University of Virginia), on the right hand side. The closed-loop algorithm is run by the DiAs, which includes a patient interface displaying information of sensor glucose values, insulin delivery rate and two traffic light icons presenting detected risks of hypo- and hyperglycaemia, respectively. The control algorithm modulates insulin infusion by Bluetooth-mediated signals to the relay box

patient action for correction of the risky trend. According to the hybrid design, the patient had to inform the system of any forthcoming carbohydrate intake which prompted algorithm computing of insulin dose to be delivered as a premeal bolus. All of the system data were sent by the 3G key of the smartphone to a web server that was accessible by the investigators through a secured portal. This module made available remote monitoring of the AP system for safety purpose (Fig. 6.2). This pilot outpatient study was extended to more numerous patients recruited by the iAP Study group and confirmed the feasibility of outpatient closed-loop although still limited to 28 h [26]. Hence the first outpatient randomized control trial testing overnight closed-loop control vs. SAP during 40 h was performed by the same group and showed reduced risk and occurrence of hypoglycaemia with the closed-loop system [27]. Using a similar system also based on DiAs wearable platform compared to SAP during the dinner and overnight time frame, the 'AP at home' consortium reported increased percent time in target range (70–180 mg/dl) with combined reductions of percent time below and above this range under closed-loop control [28]. This outpatient experiment was extended to 5 days with overnight closed-loop at the University of Virginia and also showed improved percent time in target range (80–140 mg/dl) and reduced fasting blood glucose level [29].

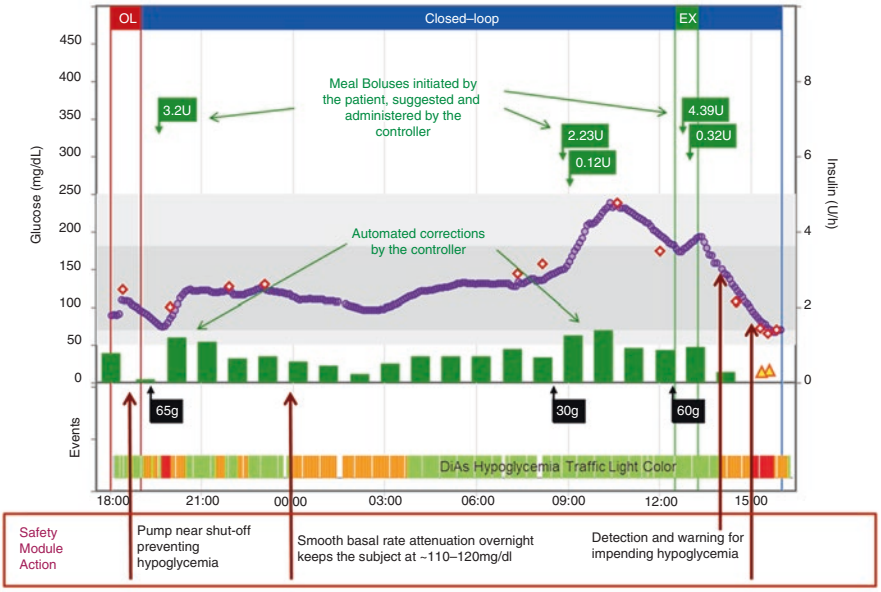

Fig. 6.2 Display of closed-loop control of blood glucose by subcutaneous insulin infusion through a model predictive control algorithm run by the Diabetes Assistant (DiAs) smartphone-based platform. This information is provided by the remote control server from 3G key transmission from the DiAs smartphone. The arrows indicate the meaning of displayed data

6.4 Home Studies with Closed-Loop Systems

Since the transitional trials had shown no safety issue with closed-loop systems, the move to home free-life studies was the next step. Overnight use for 6 weeks at home in adults and adolescents has been initially assessed in a randomized crossover study against SAP by Nimri et al. who reported a significant reduction of percent time with glucose below 70 mg/dl and an increased percent time in the glucose target range of 70–180 mg/dl [30]. Improved percent time in 70–180 mg/dl glucose range was confirmed with an overnight use of AP for 4 weeks in a multicentre study reported by Thabit et al. [31]. The 'AP at home' consortium assessed closed-loop control by a wearable AP system including the DiAs platform (Fig. 6.3) during dinner and night-time vs. SAP during 2 months and reported a significant increase of percent time in 70–180 mg/dl glucose range associated with combined reductions of percent time spent below and above this range [32]. Moreover, this study showed for the first time a reduction of HbA1c with prolonged use of closed-loop in free-life. Interestingly, glucose control on day and night was also significantly improved although closed-loop was not active during daytime. A 1-month extension of this study with 24-h active closed-loop showed a further benefit on glucose variability [33]. Meanwhile a multicentre prospective trial coordinated by the University of Virginia including sequential 2-week periods with SAP, followed by overnight AP and then full-day AP, reported similar improvements vs. SAP when AP was active [34]. Moving from overnight to 24-h AP only further reduced time spent below 70 mg/dl during day and night. This observation points to the limits of the hybrid AP option in which meal management is close to that of a patient using a simpler bolus calculator. Hence improving glucose control during daytime by closed-loop vs. SAP is difficult to achieve.

A longer outpatient AP experience was reported by the 'AP at home' consortium for 12 weeks in adult, children and adolescents [35]. In this study closed-loop was active day and night in adults and overnight only in children and adolescents and randomly compared to SAP according to a crossover design. Percent of time in the target range (70–180 mg/dl in adults, 70–145 mg/dl in children and adolescents) while using AP was significantly higher both in the adults study, 67.7% vs. 56.8%, and in the children/adolescents study, 59.7% vs. 34.4%. Similarly to previous studies, the improvement of glucose control by closed-loop was mostly due to tighter control during the night-time period.

A few months later, an extension of the multicentre prospective trial coordinated by the University of Virginia mentioned above investigated 24/7 closed-loop use up to 6 months and reported the sustained improvement of median time in target glucose range which was 77% against 66% at baseline [36]. Median time spent below 3.9 mmol/l remained significantly lower at 1.3% vs. 4.1% at baseline. Mean HbA1c levels moved from 7.2% to 7.0%, with a significant relationship between the use of closed-loop mode and improvement of HbA1c level. Interestingly, glucose control was similar day and night although the patients perceived the benefit mainly at night-time. This study extension showed the feasibility of long-term closed-loop use. Nevertheless the patients complained about the cumbersome wearable devices in everyday life.

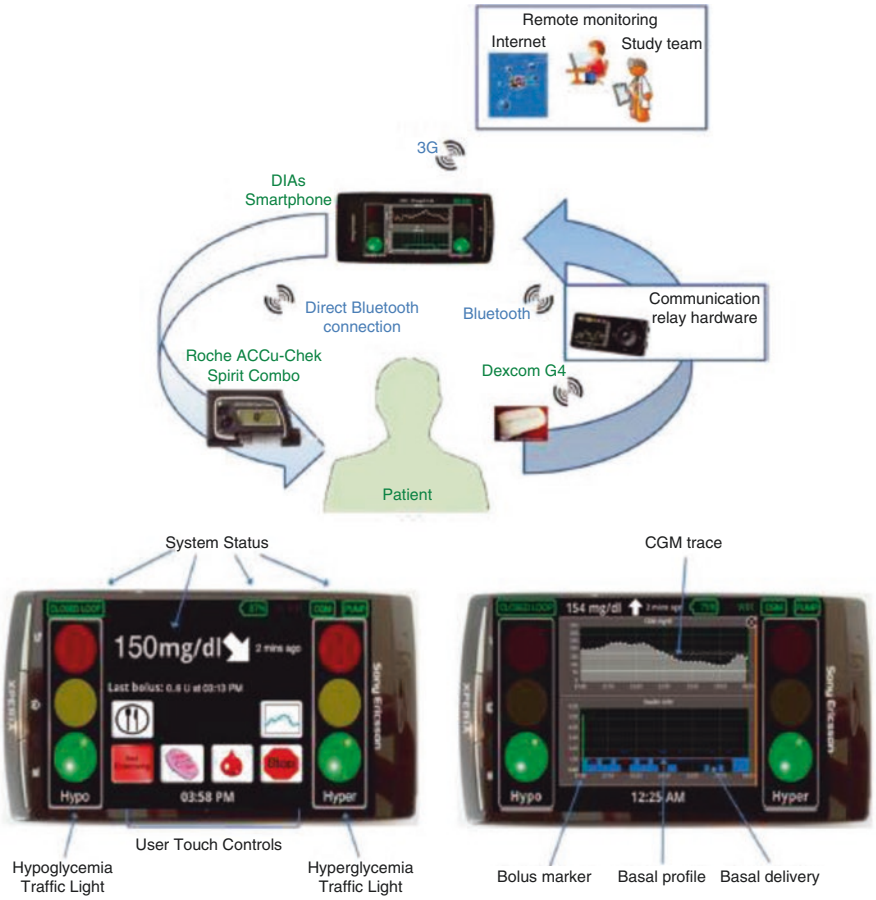

Fig. 6.3 Components of a wearable artificial pancreas system. Upper panel: system architecture. The wearable closed-loop system combines subcutaneous glucose sensing by Dexcom G4, continuous subcutaneous insulin infusion from AccuChek Spirit Combo pump and a model predictive control algorithm run on the DiAs smartphone-based platform. Insulin pump and glucose sensor communicate wirelessly with the DiAs. Lower panel: Diabetes Assistant (DiAs) user interface. CGM, continuous glucose monitoring

At the EASD meeting in September 2016, the results of a 3-month prospective 24/7 closed-loop study involving 124 patients were presented [37]. While the patients used the Medtronic MiniMed 670G system, including an insulin pump with embedded control algorithm wirelessly connected to a CGM, with a median percent time of 87.2% in closed-loop mode, sensor glucose moved from 66.7% at baseline to 72.2% for the 3 months in the 70–180 mg/dl target range, and mean HbA1c level decreased from 7.4% to 6.9%. Over 12,389 patient-days, no episodes of severe hypoglycaemia or ketoacidosis were observed. These robust safety data led to the FDA approval of this system for clinical use in the therapy of T1D, which represents a milestone in the development of closed-loop insulin delivery. The detailed results

of this study were reported a few months later [38]. Both the adolescents (n = 30) and the adults (n = 94) showed significant improvements of HbA1c levels from 7.7% to 7.1% and from 7.3% to 6.8%, respectively, and time in target glucose range from 60.4% to 67.2% and from 68.8% to 73.8%, respectively, whereas only the adults showed significant reduction of percent time below 50 mg/dl from 1.1% to 0.6%.

Following this first approved AP system for routine care of T1D, the challenge is to get a similar validation of the other developed AP systems. To reach this goal, the US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded four research programmes by early 2017 aiming at the collection of data necessary to bring AP technology to T1D patients. These programmes include:

1. The International Diabetes Closed-Loop trial, testing the control automated (hybrid) delivery system including a smartphone-based algorithm derived from the DiAs platform, led by the University of Virginia (Boris Kovatchev as principal investigator (PI)), and involving seven US centres and the Universities of Montpellier, Padova and Amsterdam in Europe.
2. A full-year trial dedicated to young T1D patients aged 6–18 led by the University of Cambridge (UK) (Roman Hovorka as PI) testing an AP system with a smartphone-based algorithm and involving four US and two UK sites.
3. A 3-month trial in young T1D patients comparing the FDA-approved AP system to a next-generation system aiming at improved control, mainly around meal time, led by the International Diabetes Center, Minneapolis (PI: Richard Bergenstal), and Schneider Children's Medical Center, Petah Tikva, Israel (PI: Moshe Phillip), involving five US sites and sites in Germany, Slovenia and Israel.
4. A 6-month study testing a bi-hormonal AP system in adults led by the Massachusetts General Hospital in Boston (PI: Steven Russell) and the Boston University (PI: Ed Damiano), involving nine US sites. Besides, other AP systems are in development by industry [39], start-ups [40, 41] and academic centres worldwide [42].

6.5 Perspectives

The last decade has shown dramatic advances in the performance of clinical trials with closed-loop systems which clearly document the feasibility of this mode of therapy for outpatients with T1D, its ability to improve time spent in close-to-normal glucose range with a reduction of risk for hypoglycaemia and its combined safety and efficacy for glucose control at night. The current questions are as follows: (1) How can we further improve glucose control toward 100% of time spent in near-normal glucose range? (2) How to implement closed-loop mode in daily care of T1D? (3) Can we extend current data to other people with diabetes (e.g. young children, patients with type 2 diabetes, pregnant women)? The following lines will try to answer these questions.

6.5.1 How Can We Further Improve Glucose Control Toward 100% of Time Spent in Near-Normal Glucose Range?

Systematic reviews of reported AP trials tell that outpatients using AP systems spend 60–70% of time in a glucose range of 70–180 mg/dl [43, 44]. These results were obtained in rather selected patients who presented an average HbA1c level between 7% and 8%, were compliant to care and were not prone to harmful glucose deviations (ketoacidosis or severe hypoglycaemia). Hence the road map for further improvement of closed-loop glucose control in this population will be based on improvements of infused insulin and devices, algorithm refinements and potentially combined drugs, including glucagon.

A remaining limitation of glucose control with closed-loop systems occurs at meal time. With currently available fast-acting analogues, meal announcement followed by a computed premeal bolus is still the only way to avoid post-meal hyperglycaemia [14]. Full closed-loop, i.e. omitting meal announcement, will only be achievable from the availability of insulin formulations which are more quickly absorbed when SC infused than current insulin analogues or through the delivery of insulin using another route, such as intraperitoneal insulin infusion. Several options of faster insulin analogues enter the clinical field such as the faster-acting insulin aspart (Fiasp) and the BioChaperone Insulin Lispro. These insulin formulations are characterized by a quicker availability for action during the 30 min after delivery and a shorter duration of action. Closed-loop trials using these new insulin preparations will assess their effectiveness on glucose control after oral carbohydrate intakes and whether the premeal bolus can be omitted. A few trials with intraperitoneal (IP) insulin had previously showed a lower post-meal glucose excursion after meals albeit still by keeping a priming premeal bolus [10]. A non-randomized experience of sequential full closed-loop trials using an MPC algorithm performed in hospital in the same patients using SC insulin delivery and IP insulin infusion through a DiaPort system (Roche Diabetes Care, Mannheim, Germany) recently reported the significant improvement of time in target glucose range from 70 to 180 mg/dl with IP insulin thanks to higher plasma insulin levels at meal times associated with significantly lower post-meal glucose excursions [45].

Expected improvements in devices include better insulin infusion sets and more accurate and stable glucose sensing. Indeed, cannulas of insulin infusion sets remain prone to transitory occlusions and insulin underdelivery. A forthcoming catheter (FlowSmart™) developed by Becton-Dickinson holds a cannula with a side exit in addition to the main tip infusion pathway [46]. This feature is expected to rescue obstacles to insulin delivery via the main track, hence allowing more constant insulin availability and avoiding high glucose deviations related to a lack of insulin delivery. Recent research also includes the development of algorithms which are able to identify a defect in insulin infusion from the increase of sensor glucose levels contrasting with ordered insulin delivery according to the control algorithm [47]. Glucose sensors have gradually improved during the last decade in terms of accuracy with a MARD which is now below 10%. However, sensor signal remains affected by variable noise which may impair insulin prescriptions by the control algorithm. Sensor accuracy may also be

reduced during its lifetime, and the stability of sensing can be impaired by chemical (ascorbic acid, acetaminophen) or physical interferences, such as pressure-induced sensor attenuations (PISAs). Recent algorithms have been developed in order to obtain smoother sensor signal, improve accuracy during function time, detect PISAs and allow predictions of glucose changes. The addition of these algorithms to the treatment of sensor signal, resulting in so-called smart sensors, has been shown to provide more reliable glucose data to the control algorithm [48]. Interruptions of transmission of sensor signal may also corrupt control decisions and should be reduced by a simpler communication of sensor signal to the insulin pump in which the control algorithm is embedded. This 'All-in-One' device concept should ease the communication process between the closed-loop components and make wearing AP less cumbersome.

In terms of design of control algorithms, the MPC option should remain the most appropriate as long as SC insulin delivery will be privileged. A recent comparison against PID design has shown the higher effectiveness of MPC in terms of glucose control [49]. Safety control modules that aim at reducing the risk of hypoglycaemia resulting from the prescriptions of the main range control module will also remain useful although faster- and shorter-acting insulin analogues may reduce their role. A recent trial in children and adolescents taking large meals and having high physical activity in a diabetes camp has shown the effectiveness on glucose control, very similar to that of a bi-hormonal closed-loop system also infusing glucagon, of a modular algorithm including this safety feature [50]. Progress in control can also be expected from adaptive algorithms that will adjust their own parameters automatically from the data collected during previous weeks [51]. Such 'run-to-run' control modules were recently investigated in AP clinical trials [52, 53]. Another option for full closed-loop control with no meal announcement includes the prediction of meal-associated sensor glucose increment according to patient habits of taking meals at predefined time periods [54, 55].

Whether adjunctive drugs may further improve closed-loop glucose control has been considered due to the previously mentioned issue of post-meal deviations. Pramlintide has been shown to delay and reduce post-meal glucose excursions [56]. A combination with liraglutide, which also reduces body weight, has been recently reported as further improving post-meal control while using lower doses of insulin [57]. The feasibility and the benefits of using these drugs on long term, in combination with an AP system, need however further investigations. In spite of the significant improvements of glucose control with the ambulatory use of an AP system ('bionic pancreas') combining insulin and glucagon infusions [58], the benefits of bi-hormonal infusion against single-hormone (insulin) delivery still raise unanswered questions. Head-to-head comparisons of these two options have been recently published [59, 60]. Trends for a reduced occurrence of hypoglycaemia overnight with glucagon infusion have been reported, while a clearer benefit has been shown at physical exercise. Whether long-term use of glucagon may generate deleterious outcomes has to be investigated [61]. Until stable glucagon solutions and dual chamber pumps are available, combining insulin and glucagon infusion represents a burden for the patient in free-life. Hence the potential benefits of glucagon infusion will have to outweigh this burden for a possible adoption on long term.

6.5.2 How to Implement Closed-Loop Mode in Daily Care of T1D?

So far closed-loop insulin delivery has always been performed in clinical trials. Expected approval for use in daily diabetes care in forthcoming years raises the question of selecting the good candidates [62]. Safe management of closed-loop systems by outpatients looks as the primary request when selecting the patients for routine AP. According to the current experience with these systems as collected during clinical trials, a proposal of step-by-step approach toward AP use in free-life looks as fulfilling safety criteria. Training to insulin pump would represent the first step. This training should include more general education on diabetes care and insulin therapy, such as self-monitoring of blood glucose, understanding of insulin dose adjustments and insulin correction doses and carbohydrate counting in food intakes. The ability to use a bolus calculator would further document patient's knowledge on insulin needs and their modulation factors (e.g. physical exercise). The second step would consist in gaining experience with CGM, including interpretation of glucose values and trends for insulin dose adjustments as well as management of sensor errors (calibration requests, need of sensor change, etc.). Final move to closed-loop insulin infusion will need a specific training on device connections, fallback solutions in case of loss of sensor signal or insulin delivery issues and reading and interpretation of machine-man interface.

Tight initial follow-up through systematic phone calls from the care team according to progressively wider time intervals and systematic reports of alarms and glucose control issues from the patients to a 24/7 safety office will need to be implemented once the patients will use AP as outpatients. Remote monitoring of AP data through their online transmission to a dedicated web server or to the cloud can be a safe option at least for the first weeks after moving to AP, although unsupervised AP management in free-life has been reported by some authors with no harmful outcomes.

The typical patient with weak motivation for diabetes care looking for a fully automated solution that will allow forgetting diabetes will unlikely be a good candidate for outpatient AP. Indeed, patient participation to the monitoring of the AP in order to identify device failures and control issues will be of utmost importance to prevent acute metabolic events.

The suggested learning pathway toward outpatient closed-loop use has been followed during clinical trials, and neither ketoacidosis nor severe hypoglycaemia has been reported while testing AP in free-life conditions. Parent involvement in the training process will be mandatory for children recruitment.

6.5.3 Can We Extend Current Data to Other People with Diabetes (e.g. Young Children, Patients with Type 2 Diabetes, Pregnant Women)?

Almost all closed-loop trials have been performed in adults or children/adolescents with type 1 diabetes until now. Only few trials have tested closed-loop insulin delivery in prepubertal children. A first one performed in a Clinical Research Centre has

shown overnight reduction of hyperglycaemia while using a PID algorithm [63]. Two recent trials using either single-hormone [64] or bi-hormonal [65] closed-loop, for 3 and 5 days, respectively, in diabetes camps have shown significant reductions of hypoglycaemia when compared to SAP or conventional pump treatment, respectively. Only the bi-hormonal closed-loop system showed an improvement of mean blood glucose level, while the single-hormone system trial reported a higher average blood glucose level. Longer trials in free-life conditions have to be scheduled to assess the true feasibility as well as the safety and the efficacy of AP use in this population for which parent assistance is needed.

Experience of AP in patients with type 2 diabetes has been even more limited. A feasibility trial in hospital has been reported by the Cambridge group in insulin-naïve patients [66]. The observed benefit of closed-loop insulin delivery was a reduction of time spent in hyperglycaemia, mostly overnight. This result was associated with higher plasma insulin levels which might have some deleterious effects on body weight on long term. Investigations are needed to assess whether closed-loop has similar benefits in insulin-treated patients with type 2 diabetes. A sustained lower glucose level in this population would indeed be of interest if obtained with a closed-loop system since failure to reach glucose target is common and may contribute to higher cardiovascular risk. A specific interest could come from the combination of a lower average glucose level with no increase of hypoglycaemia, especially for patients with a previous history of cardiovascular events.

Diabetes pregnancies are clinical conditions for which optimal glucose control is targeted. Hence closed-loop could be of high interest and benefits if improving foetal outcomes associated with maternal hyperglycaemia. Murphy et al. have reported overnight and 24-h experiences with closed-loop insulin delivery in pregnant women [67, 68]. Main benefit was a reduction of risk for hypoglycaemia and higher overnight percent time spent in the target range. A recently reported 28-day cross-over trial comparing AP to SAP in 16 pregnant women confirmed significant reductions of hypoglycaemic excursions, while mean blood glucose level and time in and above target range were similar [69]. Although encouraging, these data need further confirmation on longer time periods.

6.6 Conclusions

Achievements during this last decade have shown that closed-loop systems can be used as ambulatory, wearable devices allowing increased safety and efficacy of insulin therapy in patients with T1D [43, 44]. Current evolution includes clinical trials of long duration of at least 6 months in free-life conditions in adult and adolescent patients to further document the benefits of AP as a therapy of T1D. Besides, these systems become more patient-friendly thanks to the reduction of AP elements in wirelessly connected combo devices including a glucose sensor, an insulin pump and a patient handheld interface, the closed-loop algorithm being run either in the pump electronics or in the patient interface [70]. Further efficacy in glucose control is expected from faster-acting insulin analogues, more accurate glucose sensors and

more sophisticated algorithms that will involve artificial intelligence by automated self-improvement and personalization with time. Integration of closed-loop systems in routine care will need to revisit patient education to diabetes care at best from the diagnosis of T1D. Ultimately, technology should allow moving from external devices to implanted artificial beta cells comprising long-term implantable glucose sensors and implanted insulin pumps using the more physiological intraperitoneal or intra-portal routes. Hence artificial organ option will compete with cell therapy as two different modes of cure for T1D.

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Islet Transplantation

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7.1 Why a Cell Therapy Is Required for the Treatment of Type 1 Diabetes Mellitus?

Type 1 diabetes mellitus is an autoimmune disease leading to an irreversible ß-cell deficit responsible for a complete insulin secretion deficiency. To date, no preventive or curative treatment for type 1 diabetes mellitus has been successfully translated to standard clinical care. Type 1 diabetes treatment is based on lifelong multi-daily injections of exogenous insulin. In the last decades, considerable improvements in diabetes management have occurred: thanks to an intensive disease management and the widespread use of new therapies such as new insulin formulations and new medical devices (insulin pump, real-time continuous glucose monitoring system, improved glucose monitoring system), the overall glycemic control of patients with type 1 diabetes has improved, and the incidence of long-term diabetic complications and the mortality of type 1 diabetic patients have decreased.

Nevertheless, despite intensive insulin therapy and use of innovative technologies, a majority of patients with type 1 diabetes mellitus fails to achieve optimal glycemic control [1]. Moreover, long-term diabetic complications are still a reality for diabetic patients: diabetes mellitus remains the first cause of non-congenital blindness, end-stage renal disease, and nontraumatic lower limb amputation. Finally,

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patients with type 1 diabetes mellitus still exhibit shorter life expectancy as compared to general population [2, 3].

The major challenge for insulin therapy is to provide the exact amount of insulin at the exact time during the exact duration. If this objective is obviously difficult to achieve with exogenous insulin therapy, it can be achieved by beta-cell replacement therapy (whole pancreas organ or islet transplantation) that permits to restore a beta-cell mass with an endogenous insulin secretion closely regulated by plasmatic glucose levels. Near than 42,000 pancreas transplantations have been performed worldwide with excellent results in terms of graft survival and long-term insulin independence [4]. These metabolic results are nevertheless counterbalanced by the morbidity and the mortality associated with the surgical procedure, and islet transplantation appears as a less invasive technique more attractive to patients and diabetologists.

7.2 Who Is a Good Candidate for Islet Transplantation and Who Is Not?

The identification of islet transplantation candidates is based on the evaluation of the balance between the risks undergone by the patients in the absence of islet transplantation, the risks undergone during or after islet transplantation (islet transplantation procedure risk, immunosuppression risk, etc.), and the benefits waited from islet transplantation.

Taking this concept of benefit-risk balance into account, uremic type 1 diabetic patients with end-stage renal disease, candidate for a renal transplantation, and patient that underwent renal graft are suitable candidates for simultaneous islet-kidney (SIK) or islet after kidney transplantation (IAK). For these patients, islet transplantation takes advantage of the immunosuppressive treatment imposed by renal graft: no additive immunosuppressive regimen is required for islet transplantation, and consequently no additive immunosuppression risk exists regarding islet transplantation.

Non-uremic patients describing brittle type 1 diabetes represent the main indication for allogenic islet transplantation. This particular form of diabetes is characterized by severe glucose variability, lack of predictability, unawareness of hypoglycemic episodes, and occurrence of severe hypoglycemia. Severe hypoglycemia is associated with an alteration in quality of life [5] and a 3.2 increased risk of death [6, 7], while glucose variability is associated with a higher risk of microangiopathy progression [8]. In these conditions, the risks undergone by patients suffering from this severe form of type 1 diabetes and the benefits expected from islet transplantation are thought to overcome the risks of islet transplantation, and patients describing brittle type 1 diabetes are identified as good candidates for allogenic islet transplantation alone.

Other indications for islet transplantation exist such as islet transplantation in combination with or after lung transplantation in patients affected by cystic fibrosis [9]. Autologous islet transplantation may be proposed to patients describing surgery-induced diabetes after subtotal or total pancreatectomy.

7.3 How Organized Is an Islet Transplantation Procedure?

Islet transplantation is based on multidisciplinary competences. It requires the intervention of diabetologists for the identification of patients who may benefit from islet transplantation and for the optimization of metabolic control during the pre- and posttransplantation period. Transplant surgeons permit the organization of organ procurement and transplant procedure in some centers in which islet transplantation is done through a minilaparotomy. Islet transplantation requires a dedicated therapy cellular unit with specialized experts able to manufacture islet cell products for clinical transplantation following cGMP standards and FDA regulations. Interventional radiologists are involved in the technical act of islet infusion in the portal vein. Finally, immunologists ensure the follow-up of the immunosuppressive therapy.

Islet transplantation starts with the retrieval of the pancreas obtained from brain-dead multi-organ donors. The organ is transported to the therapy cellular unit to undergo islet isolation procedure. Islets are classically isolated using the "automated method" established by Ricordi and colleagues in 1987 [10]. To describe briefly the method, the pancreas is cleaned with the removal of the duodenum, the spleen, and the surrounding fat. The pancreas is then perfused with a solution containing a collagenase and placed in a Ricordi chamber for the digestion phase facilitated by a mechanical agitation. This step is followed by the purification step in which the islets are separated from exocrine tissues through density gradients using a COBE 2991 centrifuge. After isolation, the islet manufacturing process has to be validated and characterized through different quality tests such as the evaluation of the purity, the viability, the sterility, the number, and the functionality of the islets, allowing or not the use of islet cell products for clinical transplantation. An islet batch is considered adequate for clinical use if the purity of the preparation is >50%, if the viability is >80%, and if the IEQ amount is >5000 IEQ/kg of recipient body weight in a maximum volume of 10 ml [11]. Islet transplantation is performed through an intraportal islet infusion (Fig. 7.1) by a percutaneous catheterization of

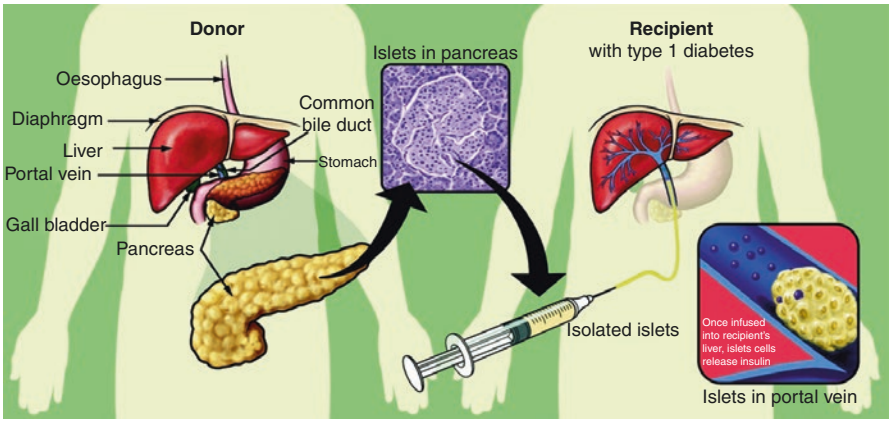

Fig. 7.1 Islet transplantation procedure (Picture from Kort H d et al. BMJ 2011)

a branch of the portal vein under ultrasound and fluoroscopic guidance or by a mini-laparotomy with a surgical catheterization of a small mesenteric vein. Two or three successive islet infusions are commonly required to reach the 10,000 IEQ/kg of recipient's body weight recommended to achieve optimal glycemic control.

7.4 Is Islet Transplantation a Successful Therapy for the Treatment of Type 1 Diabetes?

To answer this question, it is important first to analyze what are the goals of islet transplantation. Criteria defining islet graft success remained largely debated. The Food and Drug Administration (FDA) organization in its guidance for allogeneic pancreatic islet cell products [12] defined primary end point for islet transplantation as a composite endpoint consisting in a normal range HbA1c level or a substantial reduction in HbA1c associated with a prevention of hypoglycemia, independently of achievement of insulin independence. Moreover, different teams invested in islet transplantation argue that, when addressing patients with brittle diabetes, insulin independence should not be the unique criterion for the assessment of islet transplantation success [13, 14]. Recently, a consensus report in islet transplantation defined outcomes for beta-cell replacement in the treatment of diabetes: optimal beta-cell graft function is defined as an HbA1c $\leq$ 6.5% (48 mmol/mol) without severe hypoglycemia or requirement for insulin or other antihyperglycemic therapy and with an increase over pretransplant measurement of C-peptide, while good beta-cell graft function is defined as an HbA1c < 7.0% (53 mmol/mol) without severe hypoglycemia and with a significant (>50%) reduction in insulin requirements and restoration of clinically significant C-peptide production [15]. Taking into account the scarcity of organs, the morbidity of percutaneous transhepatic injection, the waiting lists, and the potential risks of HLA immunization, a realistic goal for islet transplantation should be the conversion of a brittle diabetes state to a more easily manageable diabetes state: the first goal of islet transplantation should be to release patients from severe hypoglycemia, second to improve metabolic control and prevent long-term complications, and third to improve quality of life [16].

Regarding islet transplantation efficacy, the abrogation of severe hypoglycemia associated with a restoration of glycemic stability is the most remarkable metabolic effect of islet transplantation (Fig. 7.2a, b) [17, 18]. The TRIMECO study recently published demonstrates that, when compared with intensive insulin therapy, islet transplantation is an efficient therapy to restore glycemic control and stability and protect patients against moderate and severe hypoglycemia [18]. This decrease in severe hypoglycemia incidence is associated with a concomitant restoration in hypoglycemia awareness [17]. The benefit of islet transplantation has been demonstrated to last over time with 60% of islet recipients achieving an HbA1c < 7% 5 years after islet transplantation, respectively [19].

The results regarding insulin independence have improved significantly in the last recent years: before 1999, achievement of insulin independence was obtained in less than 10% of recipients. Evolution of immunosuppression regimen, increase in

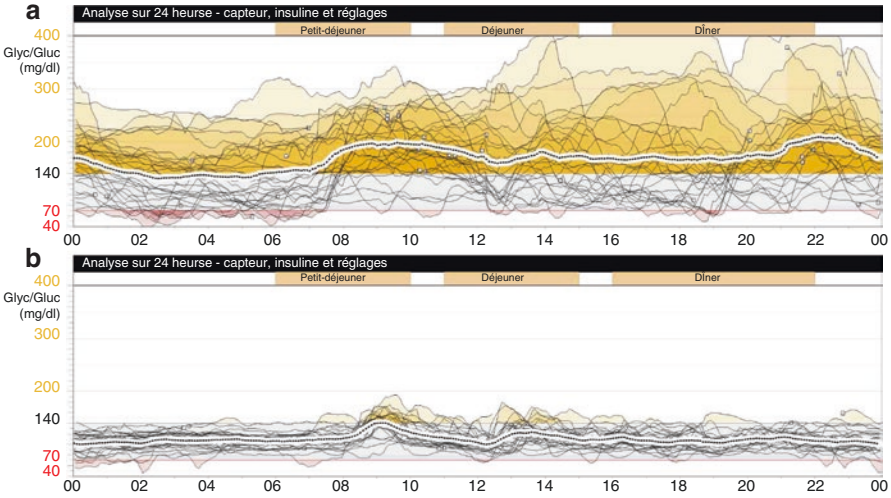

Fig. 7.2 RT-CGM in islet recipients (**a**) before and (**b**) after islet infusion (picture from LABLANCHE S, Médecine des maladies métaboliques, vol 10, n°4, pages 329–33, Juin 2016)

transplanted islet mass [20], and improvement in islet preparation quality [21] have permitted to obtain insulin independence in more than 60% of patients at 1 year in experienced centers [22, 23]. The insulin independence state fails to be maintained permanently in most of the centers [22] even if a 50% insulin independence rate at 5 years has been achieved in few centers [24]. This perfectible insulin independence rate is explained by the poor islet engraftment described in the early posttransplantation period and by a long-term islet graft dysfunction. Indeed, 50–70% of the transplanted beta-cell mass is lost in the early posttransplant period [25]: acute and chronic hypoxia, instant blood-mediated inflammatory reaction (IBMIR), and toxicity of the immunosuppressive therapy are the main factors responsible for poor islet engraftment or graft dysfunction and needed to be solved to enhance islet transplantation outcomes.

Associated with the metabolic improvement offered by islet transplantation, encouraging results have been reported regarding the positive impact of islet transplantation on the progression of diabetes-related complications. No randomized study has been performed to evaluate specifically this point, but data suggest an improvement in macro- and microangiopathy in islet recipients: ß-cell replacement seems to enhance cardiovascular and endothelial function and to reduce cardiovascular events incidence [26]. Moreover, islet transplantation is associated with a stabilization or reduction in the progression of retinopathy and neuropathy [27]. In IAK recipients, islet transplantation is described to significantly improve kidney graft survival [28]. Discordant data have been published on the impact of islet transplantation on renal graft function: different works describe a decrease in kidney function [18, 29] after islet transplantation, while others demonstrate a reduction in the urinary albumin excretion 2 and 4 years after islet transplantation [28]. In ITA recipients, discordant results have been published on the evolution of kidney

function after islet transplantation. Data from TRIMECO study evidenced that islet transplantation is associated with a decrease in kidney function in both in ITA 1 year after islet transplantation [18], while other groups report a stable kidney function in ITA after islets transplantation [30]. The positive effects of islet transplantation on kidney function may be counterbalanced by the adverse effect of immunosuppressive therapy on kidney function. Further studies analyzing the impact of islet transplantation on kidney function are mandatory to clarify the outcomes of islet transplantation on kidney function.

Closely related to the improvement in glycemic control and the abrogation of severe hypoglycemia, islet transplantation permits to increase recipient's quality of life. Insulin-independent recipients ameliorate their health perceptions and familial relationships, whereas all recipients increase their declared wellness and diabetes treatment satisfaction score [18, 27].

In conclusion, the significant metabolic improvement associated with the enhancement of recipient's quality of life and the possible positive impact of islet transplantation on diabetic complications make islet transplantation a successful therapy despite a perfectible insulin independence rate.

7.5 Is Islet Transplantation a Risky Therapy?

With a crude mortality of 2.4% over a mean follow-up of 6.7 years, islet transplantation procedure itself is described to be safe as compared to whole pancreas organ transplantation. Nevertheless, adverse events exist, and intraperitoneal bleeding represents the most common procedure-related complication occurring in the early posttransplant period. This risk has been markedly decreased by the avoidance of aspirin and the use of coils at the time of transplant but remains high (8.3% in [19] and 6.3% in [18]). The second common complication is the portal vein thrombosis becoming rare since the utilization of systemic heparin and the perfusion of limited islet cell volume. Portal vein thrombosis is described to complicate between 2% [18, 19] and 3.7% of islet infusion procedure [31]. Other complications of islet transplantation procedure are represented by transient liver enzyme elevation (50% incidence), abdominal pain (50% incidence), or severe hypoglycemia (<3% incidence).

Independently of islet infusion procedure, immunosuppressant therapy is responsible for the major adverse events described in islet transplantation. The ninth CITR annual report describes a significant decline in the glomerular filtration rate (GFR) in ITA recipient patients: ITA recipients describe a mean decrease in GFR of 12.4 ± 19 ml/min/1.73 m^3 in the 5 years following first islet infusion as compared with a mean decline of 9 ml/min/m^2 over the first 5 years in age-unadjusted cohort of 1141 patients with T1D followed during the DCCT and EDIC study [32]. This decline in the GFR is partly attributed to the nephrotoxicity of the immunosuppressant therapy driven by the sirolimus and/or the tacrolimus.

The second major adverse event is represented by neoplasm with an incidence of 3.7% (32/864 islet recipients) in the CITR report. Half of neoplasms were basal or

squamous cell carcinoma of the skin. Other complications such as increase infection risk, allosensitization, or hematologic complications (anemia, leucopenia, etc.) may be cited with few specific quantitative data available for islet transplantation.

7.6 What Is the Future of Islet Transplantation?

Islet transplantation is demonstrated to be a safe and efficient therapy to restore good metabolic control and glycemic stability in brittle type 1 diabetic patient. Many challenges currently limit islet transplantation and need to be overcome. The acute and chronic islet graft dysfunction, the poor islet availability, the risk of allosensitization, and the long-term immunosuppression are major barriers impairing islet transplantation expansion. Among developing research area, the use of unlimited alternative islet source such as porcine islets or induced pluripotent stem cells is promising with encouraging experimental data [33]. The use of alternative transplantation sites such as omental site is currently explored with the aim of developing a site guarantying a better islet engraftment and a better long-term islet graft survival. The use of immunoisolation techniques represented by macro- or microencapsulation offers the perspective of a decrease or a complete avoidance of immunosuppressive therapy [34]. All these promising approaches offer an optimistic future to islet transplantation and should permit to enhance islet transplantation metabolic outcomes and to provide islet transplantation to a larger population of type 1 diabetic patients.

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Software in Diabetes

8

Emmanuel Sonnet

8.1 Introduction

Diabetes is a huge problem in the world. The number of people with diabetes continues to grow not only in developed countries: from 415 million people affected in 2015, an increase to 642 million is projected to occur by 2040 [1]. Five million adults died from diabetes in 2015. Diabetes is a major cause of premature death, individual disability, and reduced quality of life. The estimated total cost of diabetes care is rising every year worldwide and is expected to reach more than US$627 billion by 2035 [1]. It represents a burden for individuals especially in low- or middle-income countries and for national health systems in high-income countries.

For health care providers and patients, supporting diabetes is now a big challenge. Firstly, health care providers may not be solicited, or may be solicited too late, when complications are advanced and cannot be prevented. Furthermore, the number of patients managed by a health care provider can be high. Diabetes is a chronic illness for which treatment is complex and original: education of patients concerning their disease and the use of therapies such as insulin and lifestyle interventions are necessary. But the intervention of health care professionals is limited. For this challenge, a new hope is the use of new technologies.

Software is defined as a program aimed at directing the operation of a "computer." In recent years, a lot of software has been developed to aid diabetes management (DM). This software has been offered to health care professionals and patients. The type of "computer" has now evolved. At the beginning, software was put on a desktop or laptop computer, then these programs became accessible on the internet. The latest revolution has been the development of specialized software for smartphones, and now smartwatches, called "apps." The use and availability of smartphones have rapidly increased in recent years. In 2016, the total number of users of

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smartphones worldwide was estimated to be 2.08 billion and was predicted to rise to 2.6 billion by 2019: 96% of the world's population over 6 years old will use a mobile phone in 2020 (89% in developing countries, 128% in developed countries) [2]. Close to one out of five individuals with a smartphone has downloaded a health app, resulting in the prediction of 142 million downloads by 2016, resulting in easy access to DM software nowadays.

The use of DM software is a good example of mobile health (m-health). m-Health can be defined as a medical and public health practice supported by mobile devices, such as mobile phones, patient-monitoring devices, personal digital assistants (PDAs), and other wireless devices. m-Health is a part of e-health. e-Health has been defined by Mitchell as being "much broader than telemedicine or telehealth. It covers the use of digital data transmitted electronically—for clinical, educational and administrative applications—both locally and at a distance." For the World Health Organization (WHO), e-health is "the transfer of health resources and health care by electronic means. It encompasses three main areas: (1) the delivery of health information, for health care professionals and health consumers, through the internet and telecommunications, (2) using the power of internet technologies and e-market to improve public health services, e.g. through the education and training of health workers, (3) the use of e-market and e-business practices in health systems management." All aspects of e-health are relevant to diabetes (Fig. 8.1). Some domains are discussed in other chapters (e.g., telemedicine, serious games).

By their use, types of DM software, especially apps, can be considered as medical devices, with the same properties as a drug, given that a drug is a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease. The US Food and Drug Administration (FDA) defines a "device" as

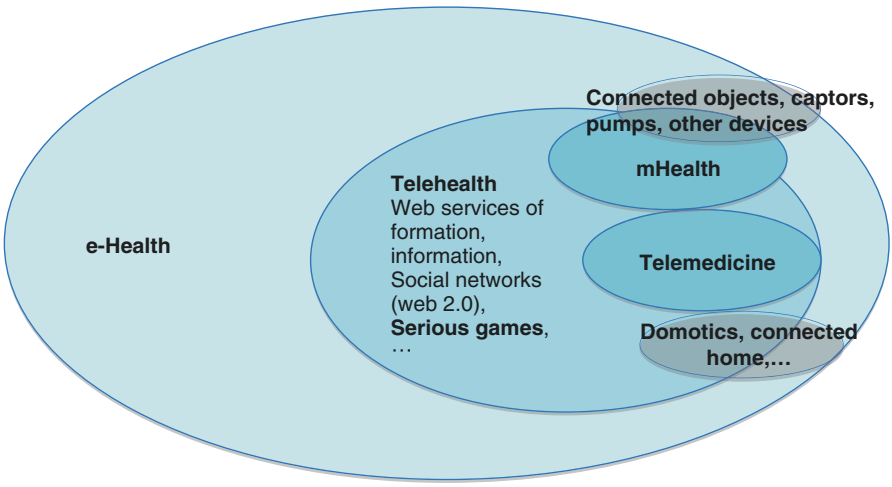

Fig. 8.1 Main domains of e-health (applied to diabetes) (modified from "Santé connectée : de la e-santé à la santé connectée. La le Livre Blanc du Conseil national de l'Ordre des médecins. Janvier 2015.")

including instruments and objects intended for the same use [3]. This new type of therapy, based on the use of DM software, is called "software prescription therapy." Thus, it is suggested that DM software should be regulated as a drug. In the USA it is now considered that the FDA has authority over these m-health products that perform core medical functions.

8.2 Types of Diabetes Management Software

8.2.1 For Health Care Professionals

DM software for health care professionals was the first type to be developed and used in clinical practice.

Software involving the intervention of a health care professional for medical management at distance from the patient can be considered telemedicine support and will not be discussed in this chapter.

8.2.1.1 Software for Analysis of Data (Glycemia, Insulin Dose, etc.)

DM software was first developed for aiding the analysis of data issued by medical devices. These devices include insulin pumps and blood glucose meters, but also continuous glucose monitoring systems, insulin pens, and new connected objects. Software can be developed for only one type of device, one model, or one industrial brand. These large numbers of different types of software (and the electrical cables required to unload the data to a computer) make their use difficult in clinical practice, so DM software is now developed to be compatible with many devices (e.g., Diasend®, Glooko®).

Software linked with a blood glucose meter can have many purposes: first, it shows real data (we all know that the reliability of blood glucose monitoring by patients in a paper logbook can fluctuate); second, it can improve the efficiency and accuracy of health care professionals' practice [4]; and third, the use of proposed graphs can facilitate dialogue with the patient. The ambulatory glucose profile (AGP) has recently been proposed as a standardized method for glucose reporting and analysis [5].

Software linked with an insulin pump which can integrate blood glucose and meal data is useful in clinical practice.

8.2.1.2 Software Aiding Clinical Decisions and/or Prescription

DM software has been developed to guide clinical decisions and/or prescription. Such support software is designed to help health care professionals in clinical decision making. Software-guided intensive insulin therapy in the critically ill or software guidance for treating diabetic ketoacidosis in an emergency department are examples. DM software algorithm models are largely proportional–integrative (PID) ones but can also be based on model predictive controls (MPC) [6]. These types of algorithms are used in integrated-sensor augmented insulin pumps. Furthermore, their use in community pharmacy is limited.

8.2.1.3 Data-Mining Software

Another type of software is represented by *specific applied data-mining software*. It can analyze large quantities of data and patient-related information. These data sets are various: blood glucose monitoring, health care events, genomics, food intake, physical activity, etc. [7]. The process can be descriptive or predictive. With the new era of Big Data, this type of research is expanding and surely will aid DM in the future.

8.2.1.4 Physician-Directed Apps

Physician-directed apps for mobile phones are available. They are not numerous and for the most part they just offer a compilation of knowledge: recent information, articles, formulas, or decision trees.

But recently, new apps have appeared to help the physician in the diagnosis of diabetes complications. For example, the usefulness of automated analysis by cloud-based software for smartphone-based fundus photography to screen for sight-threatening diabetic retinopathy has been reported [8], as has measurement of cardiac vagal tone by an electrocardiogram connected by Bluetooth to a smartphone application to screen for cardiac autonomic neuropathy [9]. These preliminary studies have to be confirmed by other reports. But this mobile technology appears to be increasingly low cost and well suited for population health to detect diabetes complications.

8.2.2 For Patients

Though there are some software packages available for computers and internet-based software, DM software is mostly represented by mobile apps.

With the large dissemination of mobile technology, patient-oriented medical apps have proliferated: in 2015, more than 1175 apps were found concerning diabetes mellitus in the Apple® app store. It is difficult for patients and health practitioners to really know these apps and to update their features. Furthermore, despite the growth, medical research on these apps is scarce.

In the medical literature, some reviews have been published recently [10–12], but the classifications used, surveys of features, and aims of the studies differ.

Most of these apps are free. Some are available in a “lite” free version, yet the complete version is not free. They are developed mainly for both type 1 and type 2 diabetic patients, but a small number of apps are designed for a more restricted population (children, pregnant women, elderly patients, etc.).

Apps are mainly developed by industrial manufacturers to complement the use of certain devices such as blood glucose meters, to increase treatment compliance, or for marketing reasons. They can also be developed by start-ups composed in part by patients and/or health care professionals, or by institutions (universities, hospitals, etc.).

8.2.2.1 Logbook Software and Insulin Treatment

Most of these apps are self-monitoring electronic logbooks. Data on blood glucose are collected (directly from the meter or not), but also data on insulin, other

medications, physical activity, and diet. Other features can be present: an integrated bolus calculator; educational programs; games; and connection with a community, a social network, or a health care professional. These apps can track and visualize health information or send automated messages. Although they are numerous, only a small number of them have been well evaluated [13].

Recently, some apps have been developed to help patients to titrate insulin in type 2 diabetes [14]. Some apps may play a major role in artificial pancreas development and specific web-based algorithms are used to predict glycemia and deliver insulin to type 1 diabetes patients with subcutaneous insulin pumps and glucose sensors [15].

8.2.2.2 Software for Lifestyle Interventions

The second type of software is represented by apps aimed at management and changes of lifestyle. Up to 90% of individuals with type 2 diabetes are overweight or obese, which is associated with high risks of diabetes and cardiovascular disease. Lifestyle interventions have proved to be effective in both prevention and control of diabetes. Exercise apps use data collected by the patient or by an accelerometer or a GPS system on a phone or a connected watch. Diet apps can feature a nutrition database, provide nutritional ratings, suggest healthier dietary choices between recipes, or scan barcodes on food packaging. There are a large number of nutritional tracking mobile DM software apps which can be used in cases of diabetes [12]. Other apps to manage other cardiovascular risk factors exist, such as apps for lipids or blood pressure management.

8.2.2.3 Educational Software

This type of software includes educational apps, with teaching and/or training methods and features (videos, animations, games, surveys, collected reference documents). These apps have the potential to increase access to self-management and improve outcomes if used effectively.

8.2.2.4 Communicative Software

Communication with a community of diabetic patients is the main purpose of certain apps or may be included in other apps, as described previously.

8.2.2.5 Other Types of Apps Available in Different Stores

Some apps have a specific purpose, such as apps that show a message on the phone of a patient in the event of a medical emergency.

8.3 Evaluation

Works whose aim is evaluation of the use of DM software are scarce, but this step is essential. The use of DM software can have many advantages: it can facilitate the analysis of data, reduce medical errors, generate new potential data and information, and increase the ability and empowerment of patients. But this use can also

have some disadvantages: higher costs of initial development, deployment, and maintenance activity; difficulty in using DM software and informatic systems on the part of health care professionals; and time-consuming use to the detriment of interactivity with the patient.

For this assessment, it is important to differentiate the evaluation itself from use of the evaluation of the results.

8.3.1 Evaluation of Use: Is the Software Really Used?

It is really difficult to assess the use of DM software by health care professionals. Though a large proportion of these types of software coupled with medical devices have real interest, they cannot necessarily be systematically used, because of lack of time, lack of the latest version of the software, or lack of the relevant electrical cables or other necessary materials. Furthermore, health care professionals may not know of the existence of such software. This particularly concerns apps, which have dramatically increased in number. One can note that many apps are developed for marketing reasons, not to resolve a medical problem. Thus, many apps are not really interesting for the purpose of medical practice. However, the opinion of the health care professional is essential for the patient; his or her advice greatly influences patients' use and compliance of these apps, as was shown in a recent French market study done by a French association of diabetic patients [16].

The extent of diabetic patients' knowledge on the use of DM software, especially apps, is also unknown. Market studies have shown that "health" and "lifestyle" apps still represent a relatively small share of all app downloads (5%), but it should be noted that the total number of app downloads in 2015 reached 200 billion. Patients with chronic diseases download apps more than the rest of the population. In the USA, a recent study showed that 12.3% of respondents with diabetes reported using health apps two or more times per day, and 15% of them had 1–5 health apps on their smartphones [17]. We can suggest, as was shown in France, that a larger percentage of patients with diabetes own smartphones than other patients, download more apps, and have greater trust in m-health [16]. The percentage of diabetic patients who download a health app is slightly but surely increasing. The knowledge of these apps seems to be spread more by word of mouth between patients than via social media or health care professionals.

In the literature, the proportion of use and compliance with of DM software is generally good during the time of the studies, but the proportion in long-term use is unknown.

8.3.2 Evaluation of Results: Does the Software Really Work?

Reports describing evaluation of one type of software after another hold little interest. First, it is impossible for them to be exhaustive because of the large number and

constant evolution of these types of software (especially apps). Second, only a few of these types of DM software have been evaluated in a published study. Third, it is difficult to generalize the results of these evaluations, because the numbers of participants are often small and the aims of the studies and the software differ, so reviews and meta-analyses give more interesting results. Fourth, many of the studies have had a number of limitations. Not all of them were randomized controlled trialsor double blinded. Some of the control groups received potentially active interventions that may have reduced the apparent effectiveness of the software. Some of these studies were of a pre–post design.

The main criterion used is variation of hemoglobin A1c (HbA1c) levels. In type 2 diabetes, software-based diabetes self-management has small beneficial effects on HbA1c levels: −0.2 to −0.8% [18, 19], at least in the short term (<12 months). Results in the mobile phone use subgroup are better (−0.5%). In type 1 diabetes, the results are mixed but appear promising: −0.3 to 0% [19, 20], even in specific groups such as children and adolescents [21]. In this pediatric group, some studies suggest a potential role in supporting self-management, with the positive effect of peer-to-peer support [22].

In all cases, more interactive tools combined with health care provider intervention result in greater clinical improvement [23]. Providing feedback and prompting behavior appear to be critical elements in behavior change for both health care professionals and patients. Some areas may require more intensive or face-to-face input. The benefits seem to be greater with mobile apps than with other types of DM software. This finding may be related to convenience, the intensity of the interventions, feedback on performance, prompts for glucose monitoring, or the behavior change techniques used by the interventions.

The effectiveness of software use in education, weight control, and blood pressure control are more anecdotal [24]. It seems that patients who use mobile phones for nutritional tracking have lower HbA1c levels and greater insight into their lifestyle therapy than those who do not [12]. Current interventions do not appear to be effective in terms of quality of life [18].

Adverse events are rarely noted. However, they could be numerous (misinterpretation of advice, inappropriate decisions, absence of useful advice, psychological burden, etc.). In one study, one participant withdrew because of anxiety [18], and in 2012, an industrial organization recalled its diabetes app because of miscalculation of insulin doses [3]. However, in different meta-analyses, no evidence of significant adverse effects has been observed.

Cost effectiveness is rarely studied [19]. The small beneficial effect on HbA1c levels could be important provided that an app is used at a very low cost in a large population. It is supposed that DM supported by digital health solutions could reduce total treatment costs: FDA-regulated digital solutions, including devices and software applications, are predicted to save billions of dollars in US health care, from US$10 billion in 2015 to US$50 billion in 2018 [25]. This reduction could be explained by elimination of the need for intervention or a decrease in intervention by a health care professional, e.g., saving time, as has been reported in telemedicine [26].

8.4 The Future

Better evaluation of DM software use in diabetes is needed now and for the future. Potential beneficial effects on HbA1c have to be confirmed in longer-duration studies with long patient follow-up. Other benefits of such software use should be further evaluated, taking into account related side effects. Software cost effectiveness has to be confirmed, taking into account patients' benefit to risk ratios. It is important to determine which population groups will benefit the most from the use of DM software. This step is necessary for patients' use and security and for institution of software-based management by health care providers and health care systems.

The next step is software certification. There are only a few public health care systems or private national consortiums offering such certification services., e.g., FDA regulation of these types of software, which are rising in number every year, and the European Commission group brought together to create guidelines for health data quality. There is a need for standardized criteria for worldwide harmonized certification of DM software. This would facilitate interactions between health care providers and software developers, and patients' and physicians choice of DM software. Such certification should take into account not only the software content but also its use, clinical benefits, feasibility, and acceptability by patients and health care providers. This certification is absolutely necessary for apps controlling diabetes devices, with a suggested standard [27].

New directions of development are appearing now. First, more open-source devices and software, not reserved only for a certain device or a brand with proprietary rights or vendor restrictions, are emerging. Second, the presence and the role of social media are growing. The development and facilitation of social relations that link people with the same interest through the internet is the basis of the "social web" using education, gaming, and social networking websites. It represents an opportunity for finding similar users and communities in a dynamic fashion. The potential influence of social media on DM software is largely unexplored [22]. Third, the use of many different technologies and the potential of smartphones make possible new features based on "augmented reality" (e.g., Google glasses and the Gocarb® project in Europe to count carbohydrates). Fourth, other automatic data will be issued by new connected objects inside or outside medical systems (insulin pens, accelerometers, connected forks, glucose captors, etc.). These data, other than those from glucose meters, will be useful to predict glycemia and thus treat diabetes. But there will be more data from many different sources available for more patients, so a new era of diabetes will be the use of Big Data techniques. The aim will be the acquisition of new information derived from fast analysis of various data in great volumes. For a patient, the next promising level after information is predictive knowledge or wisdom about his or her diabetes, with new cognitive capabilities. For the general population, new data analysis will be possible. The Big Data deployment will bring together data-processing partners and industrial actors in diabetology and medical devices, as we can see happening now.

The active role of the patient has to be increased. It is important that software development provides real answers to a real medical problem, and not only a

marketing action. The living lab is a new research concept, based on systematic user-integrated co-creation, exploration, experimentation, and evaluation approaches integrating research and innovation processes. There are some living labs in the field of diabetes. Their influence has to be favored. Furthermore, new competencies will be developed by patients. Given the growth of e-education, e-learning, and other aspects of e-health, new expansion of literacy of our diabetic patients is necessary. This will provide patients with novel skills to access knowledge through technology and the ability to assess complex contexts, as recommended by the United Nations Educational, Scientific and Cultural Organization (UNESCO) [28]. Structured education has to be integrated into a large number of different types of DM software. All these new technologies can be applied to create new personalized features with educational content.

There will be major concerns with regard to patients' privacy and data confidentiality. Data disclosure and use should be protected by law. Industries should inform patients about how and where their data are being used.

In this revolution, what will be the place of the health care provider? The role has to be central, and not only for final evaluation or certification. The role is of primary importance in many other aspects: creation, development, counseling, therapy ("software prescription therapy"), and education of the patient in this new aspect of dialogue and knowledge. To support patients, involvement of health care providers is essential. But it is difficult to know how the use of this software will be integrated into routine clinical care or into the provider work flow.

8.5 Conclusion

In recent years, in parallel, the burden of diabetes has been growing and new technologies have appeared. Development of many different types of diabetes management (DM) software, especially apps for smartphones, has been proposed to aid the management of this disease. There are now many different types and uses of DM software available for use by health care professionals and by patients. Their role is growing, and types of DM software can be now considered medical devices. The use of types of DM software seems to have many advantages, but their real interest in clinical practice has not yet been properly defined. To date, their evaluation has only been partial but appears promising. A beneficial effect on hemoglobin A1c has been demonstrated, especially in type 2 diabetes, with use of mobile apps. The overall impression of these tools' ability to help diabetic patients with their conditions in terms of other criteria remains positive. Certification of DM software with international validated criteria is an important step to organize. Many directions of development are emerging—open-source software, social media, augmented reality, Big Data analysis, etc.—meaning that this domain is still growing. For this, an active role of diabetic patients in many aspects of development of DM software and reinforcement of patient literacy is necessary. The role of health care professionals is also essential to accompany this new aspect of therapy. Let's help patients and health providers enter a new era: the future is now.

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Telemedicine and Diabetes

9

Sylvia Franc

Among the chronic diseases, diabetes is especially amenable to remote monitoring by telemedicine. Further, diabetology is the leading medical specialty in terms of volume of publications regarding telemedicine in Medline [1]. While the value of telemedicine has already been demonstrated in screening for diabetic retinopathy and/or follow-up of diabetic foot lesions, most of the studies in telemedicine with regard to diabetology continue to focus on remote blood glucose measurement via telemonitoring. In this case, patients transmit the data necessary for their follow-up, either automatically or manually, to a healthcare professional, who then interprets them remotely and sends back comments to the patients by text message, email or teleconsultation (Fig. 9.1a). The prominence of telemonitoring is partly due to the data transmission capacity of technologies, which facilitates the monitoring of clinical and laboratory parameters and the transmission of appropriate alerts. However, such systems have their limitations: they can be extremely time-consuming for healthcare providers who must analyse the data, and the time lag means that the comments are generally of little practical value to patients. A more elaborate form of telemedicine however is currently being developed with the aim not only of transmitting data but also of processing this data and enabling the caregiver to provide targeted assistance (Fig. 9.1b) [2]. This form of telemedicine is now moving out of the experimental stage and towards large-scale development and integration in patient care.

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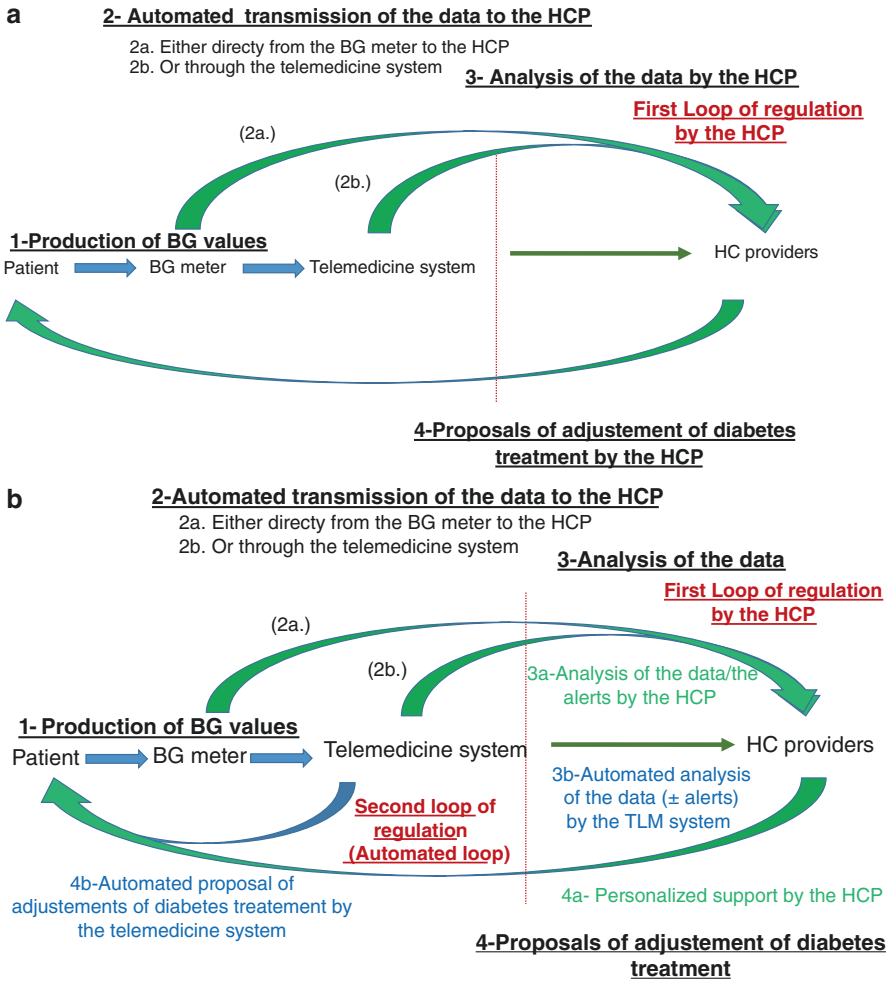

Fig. 9.1 Steps in a telemedicine system, from Klonoff et al. [2]. (**a**) A standard telemedicine system focused on remote telemonitoring. (**b**) An advanced telemedicine system with two loops of regulation

9.1 Results of Evaluations of Telemedicine in Diabetes Care

The results of the initial meta-analyses have proved somewhat disappointing for telemedicine in comparison with standard care (Table 9.1). Like all meta-analyses, these include studies and devices of heterogeneous quality. The latest publications appear to show slightly better results.

In all cases, the firm evaluation criterion remains HbA1c. However, particular attention should be paid to the following: (1) initial HbA1c level, with greater benefits being seen with higher initial levels, and (2) intervention time, with the shortest

Table 9.1 Key meta-analyses in the field of diabetes

Authors	Mean difference in HbA1c	Types of study	No. of patients (*n*)	Populations
Farmer et al. [3]	−0.1% 95% CI [−0.4 to 0.04]	9 RCTs	636	Mainly T1D
Verhoever et al. [4]	−0.03% 95% CI [−0.31 to 0.24]	6 RCTs	435	T1D or T2D or both
Polisena et al. [5]	−0.22% 95% CI [−0.35 to −0.08]	26 studies (12 RCTs)	5069	T1D or T2D or both
Marcolino et al. [6]	−0.44% 95% CI [−0.61 to −0.26] $p < 0.001$	13 RCTs	4207	T1D or T2D or both
Liang et al. [7]	−0.5% 95% CI [−0.3 to −0.7]	22 studies (11 RCTs)	1657	T1D or T2D or both
Su et al. [8]	Hedges' $g = -0.48$, $p < 0.001$	55 RCTs	9258	T1D and T2D or both

RCT randomised clinical trial

study duration generally being associated with the clearest benefits [8]. Because of the trend of decreasing intervention impact over time [6], it appears that contact through telemedicine and positive motivation should be intensified overtime. Regarding the study populations, while certain studies have shown more favourable results for telemedicine in T2D [7, 8] others have reported greater efficacy in T1D [6]. This could be associated with the type of intervention concerned: interventions that include changes in patient prescription through telemedicine are associated with better HbA1c reduction than those that do not [6].

The difference between T2D and T1D in terms of how telemedicine can facilitate disease management is determined by the therapeutic goals. For T1D patients, the focus is on determining the proper insulin dose. T2D patients, especially in the early stages of the disease, can be more reactive to lifestyle changes revolving around physical exercise and diet, which can be taught or reinforced through telemedicine. In both types of diabetes, if we leave aside the educational programmes provided online, the experiments performed in telemedicine range from telephone consultations, the simplest type of study, to DSS (decision support systems) the goal of which is automatic treatment adjustment.

9.2 Telemedicine in T2D

9.2.1 Telephone Consultations and Similar

Older short studies have shown that remote follow-up of diabetic patients involving phone calls by a nurse improved glycaemic control. Although teleconsultations are still widely used, they are now generally associated with telemonitoring. In the study by Oh in 2003 [9], over 12 weeks, patients transmitted details on BG, diet and exercise via a diary, which was further analysed by a dietitian, and subjects were

subsequently instructed about the results by a nurse via phone counselling or email. The results militated clearly in favour of phone counselling (HbA1c: −1.8%).

However, large-scale studies have not proven as clear-cut. Within the European RENEWING Health project, a study in Norway to assess use over 1 year of the few touch application (FTA) self-management system combining a mobile telephone and a blood glucose meter with automatic data transfer via Bluetooth, with or without phone counselling by a nurse specialised in diabetes, showed increased capacity for self-management, but the decrease in HbA1c recorded after 1 year did not differ from that seen in the control group [10]. However, the intervention of the specialised nurse was of low intensity (five 20-min phone calls (one/month), during the 4 first months of the study), and rather general, stressing the importance of the quality of the relationship. The meta-analysis by Wu et al. [11] specifically examining the effects of telephone follow-up interventions on glycaemic control in patients with T2D showed weighted mean differences of −0.44 (95% CI −0.93 to 0.06) in favour of telephone follow-up intervention. Subgroup analysis of more intensive interventions showed a greater benefit (−0.84%, 95% CI [−1.67 to 0.0]), indicating, as expected, that more intensive modes of follow-up may have better effects on glycaemic control, with the frequency of contact between patients and doctors being a key factor for success, although the cost of such interventions and caregiver availability are clearly limiting factors. The extension of telephone follow-up interventions to large populations without increasing costs has resulted in attempts to rationalise caregiver time.

9.2.1.1 Recourse to Non-treating HCP Supervised by a Specialised Diabetes Nurse

In the study by Walker et al. [12] in 526 T2D patients with baseline HbA1c of 8.6%, a telephone intervention from a health educator supervised by a certified diabetes educator nurse was tested vs. the mailing of print self-management materials (no calls). This study showed modest results favouring telephone intervention, with a 0.40% (95% CI [−0.10 to −0.70], $p = 0.009$) difference in HbA1c between the two groups at 1 year. However, such interventions are only effective where diabetes is not too uncontrolled. In the study conducted in Salford, UK, involving a call centre with telecarers, the latter being managed by a specialist diabetes nurse [13], subgroup analysis showed that only in fairly controlled diabetes (HbA1c 7–9%) was a modest improvement in HbA1c recorded (−0.49%).

9.2.1.2 Focus of the Nurse on Patients Identified as the Most Distressed

The problem here is to identify this patient subpopulation. In a randomised study conducted in the USA, involving 248 veterans with diabetes, the intervention group received a series of automated telephone assessments to identify the most distressed patients likely to benefit most from targeted intervention by a nurse (telephone monitoring) [14]. However, such intervention in this population showed no significant benefits regarding metabolism. This disappointing result may be due again to the general nature of the intervention or the brief patient contact (6 min/month/patient) but also to failure of the method to identify the most distressed patients.

9.2.2 Systems Focused on Data Transmission and Telemonitoring

Numerous systems have been developed to provide a variety of data to the care provider for the management of diabetes and potential associated risk factors. The main goal of these devices is to facilitate interaction with the care provider, who can then contact the patient. However, these systems have not been wholeheartedly embraced by all patients (e.g. the T-IDDM project, [15]) and/or caregivers, being considered too complex. The IDEATel system provides a perfect illustration of such systems based upon data transmission and telemonitoring. It was used in a large (*n = 1665*) randomised trial comparing TM case management with standard care in older (71 years), ethnically diverse, medically underserved, Medicare beneficiaries with diabetes (HbA1c = 7.4%) residing in medically underserved areas of New York State. Patients included in the TM group received a home TM unit to allow video conferencing with a diabetes educator every 4–6 weeks mainly for self-management education and for review of blood glucose and blood pressure measurements. However, the metabolic results were rather disappointing with a difference after 5 years of follow-up that although statistically significant was not clinically relevant (−0.29% (0.12–0.46) [16]). However, the major limiting factor for the spread of such systems is cost ($3425/unit in 2006) [17].

Dedicated websites have also been developed focusing on data transmission. Using the MyCareTeam diabetes care management application, patients could upload their blood glucose data from their glucometer and manually enter other data (blood pressure, vital signs, weight, calorie intake and exercise) to a secure central database integrated with the clinic's electronic health record. The website had an internal messaging system for patients to communicate with the care manager. Based on their data reviewed, providers could contact patients and make adjustments in their treatment plan [18]. A RCT demonstrated lower HbA1c over 12 months (−1.6 ± 1.4% vs −1.2 ± 1.4%, $p < 0.05$) compared to education and conventional care. Interestingly, greater numbers of website data uploads were associated with larger declines in HbA1c (highest tertile, −2.1%; lowest tertile, −1.0%, $p < 0.02$). Thus, provided a quick interaction between patient and HCP, web-based care management can be a useful adjunct in the care of patients with poorly controlled diabetes mellitus [19].

In all of these instances of data transmission, it is in fact the caregivers who adjust the treatment, which again raises the issue of their availability and of treatment costs.

9.2.3 Automated Clinical Decision Support Systems (CDSS)

These systems are designed to adjust treatment on the basis of a predetermined algorithm and without the direct intervention of the caregiver, have therefore been developed in T2D but with rather disappointing results at the moment as most often, no improvement over the control group could be demonstrated [20].

Smartphones. Although web ink systems have yielded interesting results, the future of telemedicine is clearly in smartphones and associated apps. Cellular phones are widely used across socioeconomic groups, and their technical capabilities (including text messaging, internet access, applications and the ability to connect to sensing devices) are continually being enhanced, making smartphones a promising means for healthcare delivery. Many applications have been developed for diabetes management. As previously, most of the systems consist in a single-loop system (Fig. 9.1a). Although the cost of these apps is lower than that of a dedicated telemedicine system, the amount of caregiver time involved remains a limiting factor. Some teams have sought to *develop a further automatic feedback to the patient (second loop, automatic)*. Such is the case of the WellDoc Diabetes Manager "Bluestar" system, the only "app" to have received FDA clearance for the management of adult T2D patients and which is now marketed in the USA. It consists of software integrated in the patient's smartphone and linked to a web portal. Glucose values are uploaded from the monitor via Bluetooth, and all of the data taken together allows the identification of different profiles and situations, which then generate an automatic message in real time from among a base of 1000 preset automatic messages that are either educational, behavioural or motivational in nature. If the system does not propose any therapeutic adjustment, all of the data may be transmitted to a secure website accessible to the caregiving team, who can then propose the necessary adjustments. In patients followed by a general practitioner and with chronic imbalance (HbA1c = 9.4%), this system demonstrated significant improvement of 0.9% at 1 year versus the control group [21].

Towards integrated management. Management of T2D patients depends upon changes in lifestyle (increased physical activity, dietary changes) that may be taught or reinforced through telemedicine.

While systems like AiperMotion500, which records physical activity levels and information about food consumption and provides motivational feedback based on energy balance, could meet this requirement, the results are still not satisfactory. Thus, a 12-week study in 27 overweight or obese T2D patients has so far not provided any conclusive data regarding the metabolic benefits [22], which means that such therapeutic systems still have to be improved. Finally, a version of the Diabeo system has been customised specifically for T2DM patients. This system, geared towards patients inadequately controlled by OADs and in whom the introduction of a basal insulin injection at bedtime is warranted, was adapted to provide automated proposals for insulin dose based on an algorithm preset by the physician. However, its chief value remains educational coaching to provide patients with advice on diet and physical activity by way of automatic messages for blood glucose values falling outside the target range. This system, evaluated in the multicentre Telediab-2 study, demonstrated a 0.5% improvement in HbA1C at 4 months compared to the control group and, significantly, twice as many patients under 7% at 13 months [23].

9.3 Towards High-Technology Solutions in T1D

9.3.1 Phones Consultations

The Diabetes Control and Complications Trial (DCCT) had already shown that increased follow-up combining monthly consultations and regular telephone calls improved blood glucose control, although it was not possible to assess the specific contribution of telephone calls to such improvement [24]. More recently, regular telephone follow-up of 46 patients treated with insulin and having diabetes poorly controlled over a 6-month period demonstrated significant improvement in HbA1c (−1.3%) [25], although this requires considerable caregiver time, equivalent to a part-time job.

9.3.2 Web-Based TM Systems Focused on Data Transmission

Web-based TM systems focused on data transmission led to rather disappointing results. With the DIABTel system, patients can load blood glucose values directly from their glucometer to a palmtop device, then from that device to their physician's computer, with feedback provided by text messages. However, no significant improvement could be demonstrated. Using the GlucoNet software developed in Grenoble and offered to T1D patients on pump therapy, the result was again unconvincing. Data teletransmission was carried out for both groups (treatment and control). Weekly feedback in the treatment group to enable insulin dose optimisation by the diabetologist via text message did not result in any significant improvement in HbA1c at 6 months in relation to the control group; however, an improvement was seen in the quality-of-life indices [26]. Certain studies evaluated not the impact of the equipment but rather that of caregiver feedback. In the Mayo Clinic study, all patients use the same data transmission via modem and telephone from their monitor (in this case Accu-Chek Complete) to the caregivers' computer, but it was only in the treatment group that nurses provided feedback to patients within 24 h [27]. The 0.4% improvement in HbA1c at 6 months was significant compared with the control group ($p = 0.03$), but nursing time was considerable: 3.4 h per patient (of which 2.4 h for data review, including 10 min with the clinical endocrinologist and 1 h for telephone feedback to patients), compared with 30 min for the unaccompanied control group. Given the high amount of caregiver time involved, large-scale introduction of this device, combining data transmission and telephone consultations, is not feasible.

Overall, coupling the transmission of blood glucose values with such retrospective feedback has been disappointing, regardless of the technological improvements introduced. One meta-analysis comprising seven randomised trials of T1DM adults using such systems showed statistically significant, but limited (0.4%), improvement [27]. These systems generally upload patient data, sending a mass of blood

glucose values, but do not incorporate truly effective feedback from caregivers other than increased weekly telephone contact, which is neither feasible nor acceptable in routine practice in the long term.

9.3.3 Systems with Automated Feedback

The Diabetes Insulin Guidance System (DIGS) (Hygieia, Inc.) software, which automatically advises patients on adjustment of insulin dosage, was tested in a feasibility study conducted in insulin-treated patients [28]. During the 12-week intervention period, DIGS processed patients' glucose readings and provided insulin dosage adjustments on a weekly basis. If approved by the study team (99% of cases), the adjusted insulin dosage was communicated to the patients. This resulted in HbA1c reduction from 8.4% to 7.9% ($p < 0.05$) and a 25% reduction in hypoglycaemia. While the findings indicate that automatic advice on insulin dosage adjustment is both feasible and reliable, from a practical standpoint, the stage of systematic approval by the doctor should be skipped, and the advice made immediately available to the patient.

9.3.4 Decision Support Systems

Among smartphones incorporating automated decision-making software, only the Diabeo system has demonstrated real efficacy with regard to HbA1c levels in T1D. This system, designed by CERITD with a programme development by Voluntis, incorporates three distinct programmes:

- A first programme uploaded via a secure website in the patient's smartphone calculates basal and prandial insulin doses according to target fasting and postprandial blood glucose levels and to the recommendations previously set by the doctor. The data collected in the electronic diary are transmitted to the HCP's computer towards a secure website.
- A second programme automatically analyses the data generated by the patient's electronic logbook and transmits alert messages to the patient and to designated caregivers. Certain of these are coaching messages encouraging the patient to use the system more while others are generated by results outside the target range, and others still are intended for the doctor, who may choose to modify the patient's algorithms; the final category concerns the use of the system by the patient (repeated declining of the proposed dose or underuse of the system).
- A third programme developed to help and define tasks for nurses to whom work has been entrusted by the doctor, within the context of a personalised training plan. This programme has already undergone preliminary assessment.

The metabolic improvement provided by the first version of the Diabeo system, with only the programme to calculate basal and prandial doses, was assessed in patients with chronic disturbances of glucose control in the multicentre Télédiab 1

study [29]. This study included 180 T1D patients with HbA1c > 8.0% despite basal-bolus insulin therapy, delivered either by multiple injections or insulin pump; baseline HbA1c was 9.07%. Patients were randomised to one of the three groups: a control group (G1) or two groups provided with the software uploaded to their personal smartphone, but with (G3) or without (G2) remote follow-up. Patients in groups G1 and G2 had 3-monthly face-to-face consultations; patients in group G3 were only followed up via short telephone calls every 2 or 3 weeks. After 6 months, patients in group G3 experienced a 0.9% reduction in HbA1c ($p < 0.001$) vs. the control group; HbA1c reduction in group G2, without remote follow-up, was 0.7% ($p < 0.001$). This improvement in HbA1c was achieved without any change in incidence of hypoglycaemia, whether mild or severe. The daily frequency of self-monitoring of blood glucose levels increased very slightly over the course of the study (3.29 at baseline vs. 3.57 at the end), but since it occurred in identical fashion in the three groups ("study effect"), it could not account for the improvement seen in HbA1c. It thus appears that for equal frequency of self-monitoring of blood glucose levels, the Diabeo system allowed patients to use their blood glucose readings more successfully and calculate their insulin requirements more accurately.

9.3.5 Towards Entirely Automatic Systems

A new version of the Diabeo system has been developed with the introduction of an automatic analysis system that allows large-scale scrutiny of data, with caregiver intervention being required only in the event of an alert. A 24/24 telemonitoring platform provides the requisite level of safety for the introduction of such a device. This automatic operation with the development of alerts frees caregivers from the laborious task of analysing data, enabling them to focus instead on assisting patients. Such a system is currently being assessed in the Télésage multicentre study (target: 700 patients within 2 years) and should result in the system being reimbursed by social security in France [30].

9.4 Development of Telemedicine

Adoption of telemedicine now seems certain. How has this change come about?

9.4.1 Great Technological Pressure

II-1-1 Explosion in technological tools [31]: Smartphones and tablet computers have become the most popular and widespread types of mobile device. Close to 55% of British adults claim to own a mobile phone and over a third own a tablet. In the USA, a report by the Pew Research Center found that 64% of all adults now own a mobile phone and 34% own a tablet computer.

II-1-2 Development of applications but also of connected objects: The development of apps is progressing in similar fashion. The number of mHealth apps available to consumers now exceeds 165,000. Some mHealth apps focus specifically on disease management through implementation of treatment protocols, such as medication reminders (35%). Among disease-specific apps (9%), diabetes accounts for 15% [32]. Another estimate of diabetes apps has shown that in 01/2013, there were 600 apps in the Apple Store and 480 in the Android Marketplace; in 07/2014, there were 969 results in the Apple Store, demonstrating how quickly the number of available apps is increasing [33].

9.4.2 Incorporation of Telemedicine in the Health System in Certain Cases

Certain public insurance systems such as Medicare (the US health insurance system, designed to assist patients aged over 65 years or in specific situations) have carried out large-scale studies of telemedicine but with unconvincing results at the moment in terms of improvement in glycaemic control.

9.4.3 Use of Telemedicine in Specific Populations

9.4.3.1 Pregnant Women

In a recent meta-analysis [34], telemedicine showed real benefits in glycaemic control: HbA1c −0.18% [−0.50, 0.14], and caesarean section rates were similar between the telemedicine and usual care groups. Its advantage may lie in the convenience of reducing face-to-face and unscheduled consultations. However, studies are limited, and more trials that include cost evaluation are required.

9.4.3.2 Transition Period in Adolescents

Telemedicine represents a unique opportunity for transition age youth with T1D to engage in diabetes management using the tools with which they are familiar and comfortable. Tools such as Skype have already been used, but if the experience was found to be a viable option for addressing nonadherence and suboptimal glycaemic control in adolescents with T1D and poor glycaemic control in a randomised controlled trial conducted over a 12-week period, in terms of improvement of HbA1c, the results were disappointing [35]. The reason might be due to the fact that in this case, Skype was used, not for spontaneous communication, but to deliver the behavioural family systems therapy diabetes programme by video conferencing. Other recent studies involving social media (Skype and Facebook) in T1D patients on pump therapy yielded far better results than conventional monitoring [36]. A meta-analysis reviewed a number of telemedicine interventions in adolescents with T1D including text messaging, phone and video consultation, remote blood glucose and disease monitoring, mobile phone applications and computer software [37]. The authors noted statistically significant improvement in HbA1c values in three

studies, although a trend towards improvement was observed in 10 of the 15 studies reviewed. Interventions combining technology with clinician and parental involvement were found to be the most successful.

9.4.3.3 Experiences of Telemedicine in Correctional Facilities

A number of studies have been conducted in correctional facilities. In the study by Kassar et al. [38] in 106 diabetic subjects (44% T1D), mean HbA1c was 9.3% with an average decrease of 0.5% from the initial to the final visit (mean: 3.6 televisits). Patients with initial HbA1c > 9% (n = 28) had an average drop of 1.3%. Given the high costs of transporting prisoners to healthcare facilities, telemedicine should help improve diabetes care for this vulnerable population.

9.5 The Question of User Profile

Although technology appears advantageous for some patients and HC providers, there may be some challenges with adoption and use of telemedicine systems by patient and caregivers [18]. Poor usability is one factor that may have had a negative effect on acceptance of telemedicine technologies. The area of human factor has become a key discipline in recent years. It focuses on system usability, designing system interfaces to optimise users' ability to accomplish their task error-free within a reasonable time and thus to accept the system as a useful tool.

9.5.1 Patient Profile

The question of patient profiling is generally considered more in terms of patient obstacles to the use of telemedicine. In this regard, very few actual obstacles have been identified other than unease about using technology [39]. The study of the effect of age on the use of telemedicine systems has yielded controversial results (the effect is generally neutral or even favourable in some studies).

We carried out patient profiling in the additional analysis for the telediab-1 study using the Diabeo system [40]. In its initial version (see paragraph 9.3.4), this tool had two programmes: the technological tool for dose determination and telemonitoring. We attempted to determine the profile of high-use patients, and HbA1c improved in comparable fashion in this population, whether the patients used the technological tool alone or were also followed up by a caregiver (−0.5% reduction in HbA1c in both cases); in other words, the help of a caregiver was not crucial. Conversely, in low-use patients, the patients benefiting most from the system were those also assisted by a caregiver (twofold greater reduction in HbA1c: −0.9% vs. −0.45%). The Diabeo system thus proved useful not only for fairly compliant patients with moderate glucose imbalance who used the dose calculation feature and carried out their injections accordingly but also for patients with poor blood glucose control, with major compliance problems and who appeared to benefit more from the motivational support provided regularly through frequent telephone consultations made possible by a smartphone linked to the website.

9.5.2 Caregiver Profile

Caregivers overall are usually more reticent than patients about using telemedicine. It must be said that some of these have been subject to massive influx of technology in their healthcare structures and have been forced to adapt to it; thus, involvement in telemedicine studies was simply tacked on to their standard tasks, without any reduction in the quantity of such tasks, and without any organisation of the telemonitoring work inherent to telemedicine. Under such circumstances, addition of telemedicine to carers' workload rather than substitution of certain acts is bound to fail. Moreover, the lack of organisation surrounding such technological tools, gives the impression not of mastering the technology but rather of being subjected to it, which tends to encourage rejection. Use of telemedicine in healthcare requires acceptance by caregivers. At least one study found that patients were more likely to participate in the telemedicine programme if encouraged by their healthcare provider to do so. Thus, telemedicine could perhaps strengthen caregiver-patient relations by enabling remote care for patients.

9.6 Structured Organisation with Grading of Interventions for "Optimised" Caregiving

After the meta-analyses based primarily on TS and demonstrating their relative failure, it appeared that the "missing element" was a decision support system that automatically analyses the data and provides the patient with real-time feedback, with a two-loop regulation system (Fig. 9.1b):

1. Automatic management of problems through feedback to patients via automatic advice regarding behaviour or direct adjustment of treatment (e.g. increased number of tablets or automatic adjustment of insulin dose).
2. For persistent problems, automatic alert messages (AAM) are generated to ensure caregiver intervention. The latter must not be the first-line doctor. Indeed, specialist medical time has become rare and expensive, and doctors will no doubt be unavailable to meet this increased demand. It is therefore essential that specialised nurses intervene with patients through a protocol of task delegation by the diabetologist to either correct treatment or encourage and motivate patients. With such an organisation, the majority of AMM should be taken into account, in most cases with remote intervention by the diabetes nurse. A small minority of alerts ultimately require secondary intervention by the diabetologist, which can be carried out under these circumstances.

Regarding organisation, such systems ensure accessibility to healthcare regardless of the declining numbers of doctors and define a new type of organisation, with the intervention of dedicated personnel, and grading of interventions allowing optimisation of caregiver time: doctors now concentrate on visits with patients

experiencing the greatest difficulties. However, this form of telemedicine implies new professions. Practising nurses (PNs) who have been leaders in telemedicine practice are now expected to be competent at integrating and translating telemedicine.

9.7 Demonstrating Medico-Economic Benefits

TM does not necessarily result in savings of caregiver time. Thus, in the Télédiab1 study, over a 6-month period, the total time of face-to-face visits per patient was identical in the groups without remote visits (around 1h10), and those allowed short but repeated telephone contacts (nine calls lasting an average of 7 min). However, this time appears to have been better used since patients' HbA1c readings improved by 0.9%, i.e. the same order as that of DCCT, the benefits of which with regard to the chronic complications of diabetes are well known (−39% concerning progression of retinopathy and −25% concerning onset of microalbuminuria). This reduction in morbidity should have a major bearing on cost reduction. Further, TM resulted in savings in transport costs for medical visits: in France these costs are borne by the National Social Security and in 2007 totalled 314€ annually per patient, giving a total annual diabetes-related expenditure of 6927€ [6]. Finally, the absence of travel to hospitals for these young and professionally active patients resulted in savings for travel and waiting times equivalent to almost 1 working day over the 6-month study period.

9.8 Conclusion

In order to ensure quality monitoring, telemedicine cannot be simply reduced to telemonitoring. It is necessary to have special tools allowing interaction between patients and caregivers at the right time together with assistance functions. Certain apparent obstacles such as age are removed. Indeed, patients, even the elderly, are generally in favour of telemedicine monitoring. Resistance to the use of telemedicine is principally on the part of caregivers. Many of these have been subject to the massive influx of technology in their healthcare structures, and in most cases, they have been forced to adapt to such technology, generally without any assistance. However, it is essential that healthcare providers embrace the technology; it is vital that they be involved to a greater extent in advance of the telemedicine studies and that they be allowed to create telemedicine systems with their patients according to their requirements and how they intend to use the systems. Where telemedicine meets the requirements of the caregivers, there is more chance of it being embraced by caregivers and patients alike, with more likelihood of it being adopted in everyday practice. Involving both caregivers and patients should strengthen caregiver-patient relations.

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Videogames in Diabetes

10

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10.1 Concepts and Origins

Gaming can be defined as a physical or psychic activity subjected to specific rules and dedicated to pleasure and fun. Emergence of novel technologies in the last three decades has resulted in the development of many videogames for personal computers, game consoles, tablets, and smartphones. Videogaming is an increasing entertainment activity worldwide. Videogame developers not only target children and adolescents but also adults who now represent a significant market share. Among videogames, the special category of serious games (SG) tends to grow significantly. A SG is a game designed for a primary purpose other than pure entertainment. This kind of software refers to products used by industries like defense, education, scientific exploration, emergency management, city planning, engineering, politics, and health care. In this latter setting, the neologism edutainment (education-entertainment) is also sometimes used to define this type of application that may indeed have a use for therapeutic education in chronic disease. The concept is to introduce some educational content in a videogame specially designed for this purpose: the entertainment content aims to boost adherence to the product and improve its educational impact. Type 1 diabetes has been one of the first health topics for which SG were developed. The rational was that this chronicle disease requires extensive education about self-care management and that this condition mainly affects children and young adults, a population prone to use videogames. First productions were created in the early 1980s, but main SG for diabetes were subsequently developed after the 2000s. Indeed, the release in 2002 of "America's

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Army," a SG developed by the US military department to improve its image among population, laid the foundation of modern SG. During the last 15 years, more than a dozen SG were developed for diabetes [1–3]. Most of them were developed on actually outdated platform and are no longer accessible. However, some of them are still available like "dBaza Diabetes Education for Kids" (http://dbaza.com/diabetes-education-for-kids.html), "Escape from Diab" (www.escapefromdiab.com), "Mr. Birman's File," or "Time Out" (these two latter games are available at no cost on http://gluciweb.com). Most of the SG for diabetes rely on the concept of situational problem solving: the player has to manage several diabetes situations in order to gain knowledge about diabetes management. In theory, the ultimate goal for the player is to transfer this knowledge into self-management of the disease. For example, in the SG "Mr. Birman's File," the main character (named Alex), is an investigative journalist and has type 1 diabetes. The player should help Alex to investigate the kidnapping of a famous scientist (entertainment content) while daily managing his type 1 diabetes (educational content). The adventure is indeed punctuated by diabetes management during meals, snacks, and physical activity. A diabetes simulator based on a validated metabolic model allows realistic interactivity between therapeutic decisions and glycemic consequences [4]. Based on the flexible insulin method, the player has to choose the adapted prandial insulin dose required for each meal presented as a detailed picture (Fig. 10.1). If the insulin

Fig. 10.1 Screenshot of the game "Mr. Birman's File." Educational sequence to improve dietetic knowledge and ability to choose adequate prandial insulin dose

dose performed is not adapted to the amount of carbohydrate, Alex may experiment hypo- or hyperglycemic episodes that the player has to correct with appropriate snacks or additional insulin injection. The entertainment adventure is hindered if diabetes management fails, motivating the player to perform well on the choice of insulin doses if it wants to complete the game. A scoring system allows to assess the player progression in the game and his ability to manage diabetes situations.

Apart from this type of situational problem solving games, a few other concept of serious games were developed for diabetes. "The DAILY" was designed as a prediction game, based on the ability of the player to predict his upcoming glucose profile according to his carbohydrate intake and insulin dose injection. The prediction was subsequently compared to real values, and a feedback was given to the patient [5]. "Glucoboy" integrated in his concept a reward system to increase children motivation: this game was connected to a glucometer, and the progression through the game was conditioned to the achievement of regular capillary blood tests [6]. More recently, "LuckyLuke, Riffifi in Daisy Town" was basically developed for smartphones and tablets and focused on diabetes prevention for the general population, with didactic games delivering information about healthy diet and physical activity (Fig. 10.2) [7].

Fig. 10.2 Screenshot of the game "LuckyLuke, Riffifi in Daisy Town." Educational sequence to improve dietetic knowledge

10.2 Impact of Videogames in Diabetes

Scientific evaluation of videogames in diabetes is scarce and heterogeneous. Most games have only been superficially assessed by unpublished satisfactory surveys. Few real clinical studies are available in this field, and they were generally performed on small populations, without any control group, evaluating qualitative criteria (knowledge, engagement, self-efficacy, communication, and self-care behaviors) [1]. For example, "Mr. Birman's File" was the latest game that has been evaluated in a multicentric pilot study including children and adolescent with type 1 diabetes [8]. The PedCarbQuiz (PCQ) and the Diabetes Self-Management Profile (DSMP), two validated questionnaires, were administered to the patients 1–3 months before serious game use, 1–2 weeks after first game use, and after 6 months of ad libitum use of the game. Forty-seven children were included in this trial. During this 6-month study, children used the game only 3.3 times, with a wide range from one time to 15 times. DSMP score and HbA1c did not improve throughout the study, but PCQ score increased from 31.6 at baseline to 36.0 at the end of the study ($P < 0.05$). PCQ improvement was greater in children who displayed the higher HbA1c and the weaker diabetes knowledge at baseline. This education support has improved the knowledge of children with T1D, especially concerning carbohydrate quantification and insulin dose adaptation. However, despite knowledge increase, skills to manage diabetes were not improved, as shown by the absence of improvement of both DSMP scores and metabolic control. In addition, in the satisfaction questionnaire, despite a good acceptance of the software, children declared that they did not intend to change their practice in diabetes management after the use of this game. This clear limitation will be discussed below. Other studies found similar results with moderate improvement of diabetes knowledge, satisfaction, nutritional education, self-efficacy, or communication with parents about diabetes [1]. It should be noticed that two studies had a more robust design with randomization, control group, and surrogate evaluation criteria of glycemic control. Trials assessing "The DAILY" and "Packy & Marlon" showed a significant decrease in hyperglycemic episodes and unscheduled doctor visits, respectively, but these studies only enrolled a few dozen patients [5, 9].

10.3 Limitations

The weak medical impact of serious games in diabetes care deserves some comments. Indeed, it might seem surprising that no large-scale study has assessed this type of tools in a population theoretically prone to use them. This finding reflects the limitations that must be overcome to create, disseminate, and evaluate serious games.

First, there is a major conceptual limitation in serious games. It is difficult to find the good balance between the game itself and the educational content; a game with rich educational content should not be playful and should obtain low player adherence. Conversely, a playful serious game should hinder the educational content and

finally be associated with low knowledge transfer. Game design should also be finely tailored to the target population as it was previously showed that identification may be of paramount importance for game impact: in the game "Escape from Diabetes," benefits were lower in white children compared with Hispanic and African-American players whose ethnic similarity with videogame characters improved story immersion and positive health outcomes [10]. In addition, to better engage children and adolescents in an educational process, a serious game should offer the possibility to be tailored to each treatment regimen in order to facilitate the transfer of knowledge to the management of diabetes in real life.

Second, the structural limitations are mainly represented by the technological lability of media for which the videogames are intended, requiring the development of costly multiplatform interoperable software. In addition, diabetes treatment and technologies are constantly and rapidly evolving, requiring regular and frequent updates to the software [11].

Finally, medical limitations also hinder the development and use of serious games for T1D. Health-care professionals may be reluctant to use such recreational educative tools without previous control or regulation. Indeed, there is actually no organized accreditation process for these tools regarding their design or content. The Swiss nongovernmental organization "Health On the Net" tries to address this question and offers a certification of sites and health applications according to a quality label, but this approach is not mandatory, and the certification is not internationally approved [12]. In this context, most serious games are used by patients in parallel to the usual care and are not implemented within the educational course delivered by caregivers. Unstructured use of serious games might at least partly explain the low adherence of patients to these tools. For example, "Mr. Birman's File" was created with the hope that the motivation to play would be sufficient to promote an adequate use. After its evaluation, it became obvious that its integration in an educational path would have been more effective. The difficult integration of such a tool in an existing education program is probably one of the main barriers for the wider use of serious games. This issue stems not only from technical difficulties in using these multimedia materials but also from the reluctance of caregivers with new technologies.

10.4 What's Next?

Although SG are still an emerging discipline, we begin to have more experience concerning their design, their use but also their assessment and evolution as instrument for patient's health education. We highlight below the main points that should be considered before developing a SG.

Regarding the design, because many educational tools failed and did not caught the interest of their potential users (caregivers and patients), it becomes essential to create these applications in collaboration with them, learning from their own vision of treatment's management to improve the usability itself of the game. Educational projects, as any training device, may vary according to the target and the goal

(learner, nursing educator, or funder). The team involved in the conception of the game must consider these aspects (be able to reach every user's category) to avoid the risk of creating a product not efficient and consequently not useful. The serious game is a "gamified" simulation of a very specific system: in the case of diabetes, glycemic variation, amount of carbohydrate, symptoms of glycemic drifts, or what to do facing a hypoglycemic event must be scientifically accurate. Any scenario must follow specific rules identified by medical expert, part of the project's team. The gameplay of a serious game can be very simple or very complex. This choice depends on the educational objectives. Be able to manage serious content through playful mechanisms could facilitate the learning process. Users can also complete quests or "gamified" tests, offered on an e-learning platform or in a complex adventure game, improving their learning curve while playing the game. Whatever the gameplay, design, and educational content, it's very important to keep the pleasure of playing which relies on a delicate balance between being too simple, then resulting boring, and being too difficult, with the risk of abandonment. This pleasure of playing maintains the player in the flow and improves the immersion experience.

Potential uses and deployment should also be taken into account during the design of an educational game. For example, the aim of a serious game of health prevention is to raise awareness and improve the diffusion of information by large multichannel campaigns. Such software should be attractive, intriguing, with a few specific educational objectives. On the other hand, for an e-learning platform or a therapeutic education sequence, users are in a learning context, and they expect that the game is useful, especially regarding the management and integration of all the contents. In that perspective, the gameplay can be more effective.

Clinical and financial evaluations are complex in the context of SG. Regarding clinical trials, the purpose of the study and evaluation criteria for such software should be clearly defined: quality of the game, success of the game, number of downloads, balance between fun and serious, technique, learning curve, and biological/clinical outcomes (HbA1c, knowledge, etc.) are some examples of qualitative or quantitative possible assessment criteria. The potential medico-economic impact of SG is also not easy to evaluate as standardized analytical grids hardly fit to such specific and personalized projects. Of note, the economic model for SG remains unclear, and funding to support such project is scarce.

Actually, the implementation of SG in telemedicine platforms is increasing, with the aim to reinforce therapeutic training with a tool allowing the users to safely manipulate specific medical contents. The use of SG also improves assessment regarding the patient's knowledge. Beside SG, gamified simulation and gamification should be massively developed in the near future, thanks to augmented reality, monitoring devices, smart textiles, sports equipment, and home automation. All these technological and connected devices will help to motivate patients for behavioral changes, physical activity, and treatment adherence, for example. Finally, increasing connection of new devices to social networks will also maintain motivation and promote peer support. Given the speed of technological change, other concepts are likely to emerge in the coming years for SG and related software.

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