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Review Article
Technology in Diabetes Treatment: Update and Future

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Abstract: Worldwide the number of people with diabetes mellitus is increasing. There are estimations that diabetes is one of the leading causes of death. The most important goals for the treatment of diabetes are self-management of the disease and an optimal quality of diabetes control. In the therapy new technologies, like real-time continuous interstitial glucose monitoring, continuous subcutaneous insulin infusion (CSII), electronic tools for the monitoring of therapeutic approaches, automated bolus calculators for insulin and electronic tools for education and information of patients, have become widespread and play important roles. All these efforts are related to the interaction between patients, caregivers, scientists or researchers and industry. The presentation of different aspects of new technological approaches in the present article should give more information about different technologies. However, because of the rather quickly appearance of new technologies, the presentation can only be a spotlight. Further studies are mandatory to analyze the effects and long-term benefits of each technology and electronic device. **Key Words:** Diabetes—Insulin—HbA1c—pump—hypoglycemia.

EPIDEMIOLOGY

Worldwide, it seems that diabetes mellitus will be one of the diseases causing the most important challenges in the 21st Century (1). During the past 20 to 30 years, the number of people suffering from diabetes has more than doubled (1–3). Some estimations calculated that diabetes "is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes (T2DM)" (3,4). The area with the most rapid increase of the diabetes prevalence is Asia, with China and India as the top epicenters (3). In 2015, the prevalence was about 9.1% in Europe and about 12.9% in the North American and Carribbean region (USA, Mexico, Canada, and 25 Caribbean countries and territories). There was an increasing tendency (4). A good message in this poor scenario came from South Germany and children and adolescents with type 2 diabetes: The prevalence rate in this age group is 2.30 per 100 000 persons. This number is relatively high. But, there was no further increase between 2004/2005 and 2016 (5).

TYPE 2 DIABETES MELLITUS

The reasons for type 2, the most prevalent form of diabetes, are alongside a genetic predisposition an unhealthy diet and a sedentary lifestyle. Hence, a high percentage of diabetes manifestations could be prevented or delayed with lifestyle changes. A healthy lifestyle includes the maintenance of a healthy body weight, consuming a healthy diet and staying physically active (3,4). For example, a recently published meta-analysis of 28 prospective studies revealed that higher levels of leisure-time physical activity was associated with a lower incidence of type 2 diabetes. The relationship in this analysis was curvilinear between the two factors. The authors found a risk reduction of 26% for type 2 diabetes among people who achieved about 11.25 MET (metabolic

doi: 10.1111/aor.13296

Received March 2018; revised April 2018; accepted May 2018.

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equivalent of task) hours per week (equivalent to 150 min per week of moderate activity) relative to inactive individuals (6).

TYPE 1 DIABETES MELLITUS

Type 1 diabetes seems to be an immune-mediated disease, preceded by a subclinical prodromal period characterized by selective loss of insulin-producing-β-cells in the pancreatic islets (7,8). About type 1 diabetes, the IDF postulates: "We also witness the worrying growth of type 1 diabetes in children. The trend toward more children developing type 1 diabetes has continued and now in 2015, more than half a million children are estimated to be living with type 1 diabetes" (4). Interestingly an increasing incidence of type 1 diabetes was found in some (i.e., Finland, Sweden, USA), but not all countries (4). These differences strongly suggest that modifiable risk factors are involved in the etiology of type 1 diabetes. Such risks are maybe perinatal or environmental factors which are able to cause and to trigger the autoimmune destruction of the insulin-producing cells (7). Knowing these factors would possibly lead to effective strategies for prevention of the disease. One aspect in this direction is the application of oral insulin. Comparable to vaccination against other diseases, orally applied insulin should produce an immune tolerance. However, a large multi-center trial performed in Europe, North America and Australia revealed no effect of oral insulin at a dose of 7.5 mg per day in autoantibody-positive relatives of patients with type 1 diabetes, neither in respect of prevention nor of the delay of the development of the disease (9).

MODERN TREATMENT

Following the international and national guidelines, the most important goals for the treatment of both forms of diabetes are self-management of the disease and an optimal quality of diabetes control (good HbA1c and the prevention of a high amplitude of daily blood-glucose excursions) (10–15). Briefly, most important for the treatment are patient education and the management of blood glucose. In respect to education, each patient should participate in a structured treatment and teaching program which integrates dietary advice, a personalized treatment plan including oral or injectable drugs, insulin application and dosage, aspects of lifestyle modification such as increasing physical activity and losing weight when appropriate, self-monitoring, acute complications of diabetes (hypoglycemia, coma, ketoacidosis) and long-term diabetes-related diseases (retino-, nephro-, neuropathy) (16–21). Of special interest in type 2 diabetes are "modern" drugs like glucagon-like peptide 1 (GLP-1) analog, dipeptidyl peptidase 4 (DPP-4) inhibitors or the group of sodium-glucose co-transporter (SGLT) inhibitors. Together with metformin (22), these are the only drugs clearly associated with a reduced mortality rate in prospective intervention studies (23–25). In the future, SGLT inhibitors will maybe also play an important role in patients with type 1 diabetes (26,27).

However, in the therapy of both types of diabetes, new technologies, that is, real-time continuous interstitial glucose monitoring, continuous subcutaneous insulin infusion (CSII), electronic tools for the monitoring of therapeutic approaches, automated bolus calculators for insulin and electronic tools for education and information of patients, have become widespread and have changed diabetic practice. On the one hand, it seems that these technologies are clearly able to improve diabetes therapy, quality of diabetes control, and patients' well-being, on the other hand, some aspects of treatment and therapeutic approaches are getting more complex and new aspects of therapy have to be taken into account in discussion and organization of diabetes care.

NEW TECHNOLOGY IN DIABETES TREATMENT

Technical devices concern a wide area of diabetes therapy. In the following section, some of these aspects will be highlighted.

Glucose monitoring

Continuous glucose monitoring (CGM), either in real-time (rtCGM) or intermittently (iCGM), will overcome many of the limitations accompanied with self-monitoring of blood glucose by patients or measuring HbA1c solely. It reflects in a much better way intra- and interday glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications (28). Following a Cochrane meta-analysis published in 2016 including 3383 patients with type 2 diabetes without insulin treatment, self-monitoring of blood glucose per se was associated with improved HbA1c (–0.33%), lower body mass index (BMI) (–0.65 kg/m^2) and better total cholesterol during short (≤6 months) and long-term (≥12 months) follow-up (29). Additionally and beyond the effects of the meta-analysis of Zhu et al. (29), Rodbard (30)

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reported that CGM has been demonstrated to be useful in reducing the risks of hypo- and hyperglycemia too, improving glycemic variability and increasing patients' quality of life in both type 1 and type 2 diabetes (30). These results were supported by an earlier published meta-analysis on the background of the Cochrane Library for patients with type 1 diabetes (31), as well as an International Consensus statement published in December 2017 (28). In an article from 2017, the authors recommend: "CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia" (28). Additionally, the experts suggest: "All patients should receive training in how to interpret and respond to their glucose data […]. Patient education and training for CGM should utilize standardized programs with follow-up to improve adherence and facilitate appropriate use of data and diabetes therapies" (28). Economic benefits were documented in a study from the USA (32). An additional field in which CGM seems to be very interesting and helpful is diabetes and pregnancy. During pregnancy, the glycemic goals are very narrow to reduce the risks for maternal and fetal diabetes complications. CGM may be able to help women to achieve optimal glucose values and to reduce frequently occurring hypoglycemia. However, the data on the effects of CGM use during pregnancy are still conflicting. In 2017, Polsky and Garcetti (33) reported that CGM in conjunction with insulin pump treatment is associated with improved glycemic outcome. But, in addition to technology for diabetes treatment, pregnant women need intensive standard clinical care. CGM can only be an adjunctive tool in pregnant women with diabetes (33).

Today several technical systems for CGM produced by different companies are available. There are also several ways in which a CGM works. In principle it can either be blinded to the patient or, on the other side, it can show the glucose values in real time. Mostly, the systems send data to a receiver where they are stored and analyzed. Then, the data and analyses are sent to the patient in real time (rtCGM) or intermittently (iCGM). In both models, the patient will gain regular information about their glucose values and fluctuations. The most common systems use interstitial fluid for measuring glucose levels. The systems are inserted subcutaneously and are worn externally by the user. But implantable CGM devices are also already or will become available in the near future. After insertion of the CGM system, a measurement of capillary blood glucose level using a standard method for self-monitoring (i.e., mostly finger-pricking) is mandatory to allow the CGM system an initial calibration. In some systems, regular recalibration is also necessary during the following period. The sensors of the CGM systems are approved for the use for varying lengths of time (i.e., Medtronic, MiniMed 640 G, 6 days; Medtronic, MiniMed VEO 554/754, 6 days; Johnson & Johnson, Animas Vibe, 7 days; Medtronic, Guardian Connect, 6 days, Dexcom, Dexcom G4/G5, 7 days [https://www.diabetiker.info/wp-content/uploads/2017/08/Technische-Übersicht-Insulinpumpen.pdf, 20.04.2018]; Abbott, FreeStyle Libre, 14 days [https://www.freestylelibre.de/, 21.03.2018]). Depending on the system, the technical approach, but also from user and environmental factors (like sweating), there are reports about site reactions, skin alterations, pulling off, falling off, losing

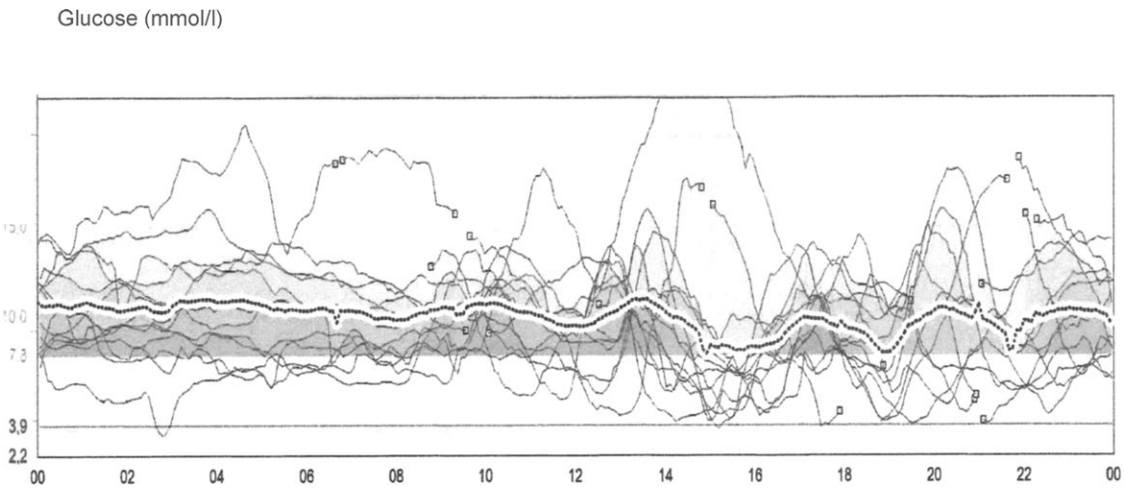

FIG. 1. Visualization of CGM values in a 35-year-old patient with type 1 diabetes mellitus for 19 years, poor glycemic control (HbA1c 8.4% [68.3 mmol/mol]) and frequently reported hypo- and hyperglycemic episodes.

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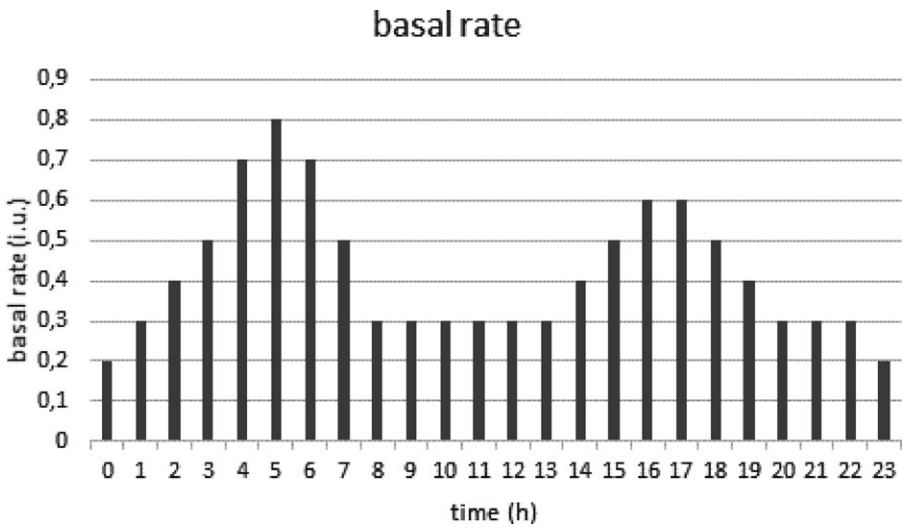

FIG. 2. Chronomodulated application of short acting insulin (human insulin or insulin analogs) as basal rate. In this patient, a little bit more insulin is given in the early morning and late afternoon, less insulin is given at night, in particular about and shortly after midnight and during lunchtime.

of the complete, or parts of the system (i.e., transmitter, receiver), transmission issues at night, malfunctioning systems and silencing of alarms. Moreover, in situations with an increase or a decrease in blood glucose levels, the CGM system can report false low or false high glucose values. The reason for this delay is the measurement of glucose levels in the interstitium which reacts slower and later in comparison to blood glucose excursions (delay of about 5 to 20 min) (34).

Up to the present, there is no identical way of presentation of the results of CGM. Each manufacturer has for its CGM system its own format for display of data. One example for data presentation in a 35-year-old patient with type 1 diabetes and poor glycemic control shown in Fig. 1. Hence, the application of the system, potential limitations, and side-effects as well as the different formats of data display support the recommendation for users (patients) and physicians to offer and participate in a special teaching program. In Germany, there is one company-independent teaching program (35). Other programs are offered by diabetes centers, companies or as "webinars" (34).

Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion (CSII) using pumps is a well-proven, efficient, and flexible method of insulin delivery (36). The first report of their use was published by Pickup et al. about 40 years ago (37). Today CSII systems consist of small, battery-driven pumps. They are designed to administer insulin subcutaneously mostly into the abdominal wall, sometimes in the gluteal area, upper legs or upper arms. In the early systems, human normal insulin was given through a butterfly needle; nowadays short acting insulin analogs are predominantly used and applied via specially designed catheters. The insulin dose is adjusted in response to measured glucose values (38). In general following an individual's circadian rhythm, a chronomodulated basal rate of insulin is given covering patient's basal insulin need; that is, a little bit more insulin in the early morning and late afternoon, less insulin at night, in particular about and shortly after midnight and during lunchtime (Fig. 2). Depending on the amount of carbohydrates the patient plans to eat, their physical activity and the actual blood glucose levels, insulin boli have to be calculated and applied individually. Fig. 3 shows a typical plan of insulin application for patient's use.

In contrast to the early days of CSII treatment, today there is good evidence and documentation of efficacy of this treatment method in both types of diabetes (39–44). For patients with type 1 diabetes Pickup et al. summarized in 2017 "There is now a well-established evidence base for the routine clinical use of continuous subcutaneous insulin infusion (CSII; insulin pump therapy) in selected people with type 1 diabetes who have failed to achieve target levels of glycemic control with the best insulin injection regimens (multiple daily insulin injections [MDI]) and structured diabetes education…" (41). In adult patients with type 1 diabetes CSII therapy is mostly accompanied by a reduction of HbA1c without a higher rate of hypoglycemia. In a meta-analysis published in 2008 and including 22 studies "a

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Plan for CSII treatment

Pat.-No.: xxxxxx
Date: 02/01/2018

Name: xxxxxxxxxxxx xxxxxxxxxxx

Type of pump	Paradigm 722					Insulin:					
Basal rate	I.U./hour					**Basal rate**	I.U./hour				
Date		23.10.				Date					
00:00 - 01:00	0,2					12:00 - 13:00	0,1				
01:00 - 02:00	0,15					13:00 - 14:00	0,15				
02:00 - 03:00	0,1					14:00 - 15:00	0,15				
03:00 - 04:00	0,1					15:00 - 16:00	0,2				
04:00 - 05:00	0,2	0,15				16:00 - 17:00	0,2				
05:00 - 06:00	0,2	0,15				17:00 - 18:00	0,2				
06:00 - 07:00	0,2					18:00 - 19:00	0,2				
07:00 - 08:00	0,15					19:00 - 20:00	0,25				
08:00 - 09:00	0,15					20:00 - 21:00	0,2				
09:00 - 10:00	0,15					21:00 - 22:00	0,2				
10:00 - 11:00	0,15					22:00 - 23:00	0,25				
11:00 - 12:00	0,1					23:00 - 24:00	0,2				
						Total amount of insulin	4,15	4,05			I.U./day

Insulin boli	Breakfast		Lunch		Dinner		At night	
Carbohydrate units								
I.U. per carbohydrate unit	0,6	0,5	0,6	0,5	0,6	0,5		
Range for optimum blood-glucoe values (mmol/l)	6				6			
Correction (Decrease of blood-glucose per I.U. insulin)	4				4			

Date:

Signature
Physician

FIG. 3. Plan of daily insulin application using CSII in a 15-year-old girl with type 1 diabetes mellitus for 4 years and an HbA1c of 6.8% (50.8 mmol/mol)

between-treatment difference of –0.4% HbA(1c) […] in favor of CSII therapy" was found. This better HbA1c was associated with lower daily insulin requirements. The incidence of hypoglcemia under CSII treatment was comparable to other treatment methods (42). In an other meta-analysis, Pickup and Sutton revealed even a reduction in hypoglycemia. They wrote in their publication "The severe hypoglycemia rate in type 1 diabetes was markedly less during CSII than MDI, with the greatest reduction in those whose severe hypoglycemia on MDI and those with the longest duration of diabetes." (43). All these results were conclusive with a recently published paper by Roze et al. (44). Here, along with the better quality of diabetes control and the lower rate of hypoglycemic events, the authors found a cost-effectiveness too ("CSII was associated with higher lifetime direct costs due to higher treatment costs but this was partially offset by cost-savings from reduced diabetes-related complications.") (44). In children

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and adolescents with type 1 diabetes CSII therapy seems also to lead to a better quality of diabetes control and an improvement in quality of life for both, the young patients and their parents (45–47). In Germany for example, up to the present, more than 40% of children and adolescents with type 1 diabetes were treated with CSII with an increasing tendency (48,49).

For patients with type 2 diabetes Pickup et al. published a meta-analysis. In this article, "CSII achieves better glycemic control than MDI in people with poorly controlled type 2 diabetes with ~26% reduction in insulin requirements and no weight change." (41). Overall, the HbA1c difference between patients on CSII versus MDI was –0.40% (–0.86 to 0.05% [–4.4 mmol/mol (–9.4 to 0.6 mmol/mol)]) (41).

Closed loop systems

Up to the present, the feasibility, safety, and efficacy of a closed loop insulin delivery system have not been fully established. In general, closed loop means that a technical system monitors blood glucose levels. On the background of this information, it uses an algorithm to determine if insulin is needed or not needed. In some models also glucagon is integrated and the system calculates if glucagon is needed or not. Insulin and glucagon are given, when it is appropriate according to the systems decision directly to the patient. In its best technical variant, a closed loop system requires no action on the patient's part, everything is done automatically by the device. Mostly, closed loop just means another term for "artificial pancreas" (50). First reviews and studies suggest that a closed loop systems is also able to reduce hypoglycemia and to increase time in therapeutic glucose range overnight and during the day (51–55). In adolescents with type 1 diabetes, Breton et al. documented identical benefits during outdoor exercise (56). These findings were supported by a further study performed by Dovc et al. (57). On the other side, closed loop systems not only promise positive outcomes: Still, there is some concern about safety and psychological impacts in daily life. In some aspects, modern technology can be associated with increased anxiety, low levels of trust about physical bulk, technical glitches, and difficulties in everyday life (58). Future research has to elucidate all these aspects in prospective, controlled trials.

Electronic teaching and applications for smart devices

During the last years, multiple digital tools and applications for smart devices have been developed with the aim to assist patients with different diseases in their treatment. A systematic review and meta-analysis of randomized controlled trials, published in March 2017, enrolled 1236 publications about the topic (59). Up to, the beginning of 2018, the number of trials along with the number of patients using electronical devices in their daily therapeutic approach seems to increase again (60,61).

In summary, electronic teaching and applications for smart devices address several aspects of diabetes treatment (59,61,62). These are:

1. Electronic teaching: Participation in structured treatment and teaching programs is strongly recommended for all patients with diabetes. It is a preliminary for an optimal self-management of the disease, along with best quality of life (17,19,21). Electronic and online learning offers new possibilities. It allows patients to have access to the learning program whenever they want, is less cost-intensive than a face-to-face learning at a hospital or diabetes center where diabetes educators and a physician have to be present, and it allows learning over long distances. The latter is of special interest for patients living in rural areas or in countries with a low density of physicians and diabetes centers. However, electronic and online learning also have some important disadvantages. Mostly there is no possibility for communication and collaboration between "learner" and teacher (diabetes educator, physician) or other peers. In general, electronic or online programs were completed in a one-on-one relationship with the computers or smartphones. This is an important limitation for reflective learning (63–66). The first studies about clinical use of electronic and online treatment programs failed to have high levels of uptake, but they also demonstrated a comparable effect to programs with conventional teaching and learning (67–70). These results may lead to the conclusion that up to the present, electronic programs are not superior, but they are rather suitable in patients who do not have easy access to participate in a face-to-face teaching and treatment programs. Moreover, electronic programs may be effective tools for refreshment of diabetes knowledge (67–69).
2. Computer-aided technologies: Computer-aided technologies (referring to websites, smart phones, insulin pumps, blood glucose meters) mostly consist of technologies to provide

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information on diabetes (self-)management, on users' disease-related knowledge, and to give feedback. However, up to the present there is a lack of high quality data about this heterogeneous field. For example, a trial published by Tokunaga-Nakawatase et al. (71) found that in patients with risk for type 2 diabetes, a "computer-based […] lifestyle intervention was effective on dietary habits, [but] only during the intervention period" (71). In a review, Health Quality Ontario (72) reported a statistically significant reduction in HbA1c of about 0.50% in patients with type 2 diabetes and using blood glucose home telemonitoring technologies (72). An American group recently published data about glycemic control in medically underserved patients. They included 13 studies with a total of 3257 adult people with diabetes in their meta-analysis. Using computer-aided technologies, the patients revealed a decrease in HbA1c between 0.36 and 0.27% (73). Interestingly, computer technology is maybe also effective in children with risk for type 2 diabetes. In respect of such a cohort, Hannon et al. (74) conclude that the "use of a computerized clinical decision support system to automate the identification and screening of pediatric patients at high risk for T2D [type 2 diabetes] can help overcome barriers to the screening process. The support system significantly increased screening among patients […] and adherence to follow-up appointments with primary care clinicians." (74).

3. Applications for smart devices:

(i) Some applications are simply able to present data. These data could include data about physical activity, eating, individuals' glucose levels, dosage and time of application of drugs (inclusive insulin), as well as further medical data, like heart frequency, blood pressure, and many other information. Other applications store the data, offer interactive use, allow an adaption toward the users' preferences and profiles and apply recommendations(59,61,62).

(ii) In respect of caloric and carbohydrate intake, there is also a variety of different applications. Some help patients with access to food databases, give nutritional information, show the carbohydrate content and assist in carbohydrate and caloric counting. Moreover, advice can be given regarding food choice, fat, salt, vitamin, and fiber content. Some applications are also able to interact with algorithms for the calculation of drug dose (i.e., insulin dose adaption) (59,61,62).

(iii) Most applications for smart devices already allow users to identify and to quantify physical activity. Additionally, some applications enable patients to monitor frequency of physical activity, time, and type. They can instruct the patients to do "good" activity and to increase frequency and intensity when a weight reduction is desirable (59,61,62,75).

(iv) Several providers also developed applications for smart devices to enhance patients' motivation, empowerment and compliance to therapy. They are able to coach patients, to improve adherence to self-control of glucose levels, to medication and insulin application (59,61,62).

Automated bolus calculators

For an optimal insulin therapy with good quality of diabetes control, patients have to estimate the amount of prandial insulin before each meal. This estimation has to be done according to several factors, including current glucose level, anticipated carbohydrate intake, insulin-to-carbohydrate ratio, estimated insulin sensitivity, target blood glucose level, and anticipated physical activity during the following and the past hours (76). According to an analysis of Sussman et al. (77), patients with insulin-treated diabetes made errors in more than half of the calculated insulin doses. Hence, poor numeracy is often associated with worse self-efficacy, low levels of self-management, and poorer glycemic control (78). Automated bolus calculators have been available for many years. Either they are integrated in insulin pumps or, in some cases, they are part of glucose meters. Looking at the literature, the effects of both forms of bolus calculators are heterogeneous too. Several studies reported a clear benefit (79–82), whereas other authors (83–86) concluded a positive effect only in special aspects. A good and conclusive summary is given in a recently published paper by van Meijel at al. (76): "Use of a bolus calculator modestly improved glucose variability […], but did not affect other parameters of glycemic control or diabetes-related quality of life" (76). However, according to Rossetti et al. (83) "Educational programs aiming to increase patients' empowerment and caregivers' knowledge are needed in order to get full benefit of the technology" (83).

PREVENTION

Following the estimations, that diabetes is one of the diseases with the most important increasing

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prevalence potential and the knowledge that in type 2 effective prevention is possible (1–4), the question arises how can modern technology help. Most persons with a risk for type 2 diabetes have a more sedentary lifestyle and are mostly overweight or obese. Hence, lifestyle interventions seems to be effective. But, primary care providers, physicians, and also the patients themselves are frequently frustrated about the lack of effort in respect to more exercise in daily life and the poor adherence to a low-caloric diet. Potential solutions are maybe the utilization of online programs and applications for smart devices to engage patients in lifestyle modification as well as similar technologies to monitor and to give support to patients' adherence. First studies have been enrolled and early results are promising (87–90). In one randomized controlled trial for example, the intervention program will be delivered via mobile phone along with weekly coach calls for 12 weeks. The system analyzes patients' weight, physical activity, and diet. These data were embedded into video lessons about the prevention of type 2 diabetes (91). A similar program was started by Schiel et al. (92,93) for children and adolescents with risks for type 2 diabetes. Also in this group and over a period of 12 months intervention, use of a mobile phone and a computerized support program along with regular phone calls was effective in respect to weight reduction and the increase of physical activity. However, future publications will bring more light to the efficacy, long-term benefit, and also economical aspects of such interventions.

CONCLUSIONS

Over the last years along with the development of new technologies, the treatment of diabetes has considerably changed. Continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII) using pumps, the combination of these tools to closed loop systems, and electronic teaching and applications for smart devices are some of the innovations. The presentation of different aspects of new technological approaches in the present article gives more information about the advantages and disadvantages of different devices.

Conflict of Interest: The authors have declared no conflicts of interest for this article.

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