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EDITORIAL

Impact of new technologies on diabetes care

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Abstract

Technologies for diabetes management, such as continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) systems, have improved remarkably over the last decades. These developments are impacting the capacity to achieve recommended hemoglobin A1c levels and assisting in preventing the development and progression of micro- and macro vascular complications. While improvements in metabolic control and decreases in risk of severe and moderate hypoglycemia have been described with use of these technologies, large epidemiological international studies show that many patients are still unable to meet their glycemic goals, even when these technologies are used. This editorial will review the impact of technology on glycemic control, hypoglycemia and quality of life in children and youth with type 1 diabetes. Technologies reviewed include CSII, CGM systems and sensor-augmented insulin pumps. In addition, the usefulness of advanced functions such as bolus profiles, bolus calculators and threshold-suspend features will be also discussed. Moreover, the current editorial will explore the challenges of using these technologies. Indeed, despite the evidence currently available of the potential benefits of using advanced technologies in diabetes management, many patients still report barriers to using them. Finally this article will highlight the importance of future studies tailored toward overcome these barriers to optimizing glycemic control and avoiding severe hypoglycemia.

Key words: Diabetes; Technology; Glycemic control; Quality of life; Outcomes; Management

Core tip: There have been many advances in the technologies associated with diabetes care in the last few years, which have resulted in new opportunities

in the treatment of diabetes. Despite the encouraging results and the prospect of a fully automated closed loop system in the near future, metabolic control remains suboptimal in most patients with type 1 diabetes. Data from registries has recently shown that a large proportion of children with type 1 diabetes does not meet the age associated A1c targets across all countries, especially in the youth age. This editorial discusses the impact of these technologies on glycemic control and quality of life and attempts to address how to overcome barriers using these technologies to achieve improved metabolic control.

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Recently, data related to the safety and effectiveness of a bionic pancreas under unrestricted outpatient conditions were published by Russel *et al*[1], reporting that "as compared with an insulin pump, a wearable, automated, bi-hormonal, bionic pancreas improved mean glycemic levels, with less frequent hypoglycemic episodes" in both adults and adolescents with type 1 diabetes, in outpatient settings. While the device is still imperfect, (difficulty with wireless connectivity, poor stability of glucagon, need for faster insulin analogues, risk of hypoglycemia and need for restrictions in food and alcohol intake) these results marked an important step toward a fully automated closed-loop system.

Currently, at least 20 research groups are working worldwide on glucose-sensor-controlled automated insulin delivery systems (closed loop pumps), and during the last years, great progress was reported in closed-loop system in outpatients settings, with a particular focus on overnight glycemic control, whereas postprandial and post-exercise glucose control remains a challenge[2-5].

These promising studies bring the artificial pancreas closer to public use, which is possible due to the recent improvements in technology for diabetes care. Nonetheless, many patients spend the majority of their day outside the recommended glycemic ranges. As a result glycemic control remains suboptimal for many patients with type 1 diabetes[6].

It has now been 10 years since the Epidemiology of Diabetes Interventions and Complications study confirmed the need to optimize glycemic control as early as possible to sustain risk reduction for micro- and macro vascular complications[7,8]. Since then, many national and international diabetes associations [*e.g.*, the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes (ISPAD)] revised their guidelines for type 1 diabetes management and now recommend a target glycated hemoglobin (A1c) of 6.5%-7.5% (48-59 mmol/mol) for most people with type 1 diabetes (T1D)[9,10]. However, recently published data by McKnight *et al*[11], reported that only 30% of males and 29% of females aged < 15 years, 24% of males and 20% of females aged 15-24 years, and 30% of males and 28% of females aged > 25 years achieved these recommended A1c levels (< 7.5% or < 59 mmol/mol). These data confirmed that this target is not easily achieved in many people with type 1 diabetes and also that A1c levels are higher in those aged 15-24 years than among other age groups across many countries[11]. It is clear that there is still a gap between patients' glycemic control outcomes and what can be achieved with newer therapeutic improvements, even if technological key advances as the continuous subcutaneous insulin infusion (CSII) and the continuous glucose monitoring (CGM) have been shown to greatly improve diabetes care.

Focusing on the effectiveness of new technologies and the limitations of the use of such technologies in the real world may help find a way to achieve the A1c goals for many patients. In addition, it could give us greater insight into barriers to sustain the use of these therapeutic advances and how to overcome them. Several recently published review studies and meta-analyses addressed these topics[12-14]. Deeb *et al*[15] assessed the association between how insulin pumps were used and blood glucose control to determine if the use of advanced pump features improved glycemic control. Indeed, over the last 15 years, it has been shown that the increasing use of insulin pump can result in many health benefits and an improvement of overall treatment satisfaction[16,17]. Thus, it would be expected to improve long-time metabolic outcome in patients using this treatment. Although randomized controlled studies and systematic reviews of pediatric cohorts using CSII showed only modest benefits (in the range of 0%-0.9%[18]) in terms of mean A1c compared to multiple daily injections (MDI), many prospective and retrospective case-control studies, clinic-based series and registries, reported that pediatric insulin pump users have a lower A1c when compared to patients using MDI, and that they are more likely to achieve A1c targets than those on injections. Recently, Olsen *et al*[19] showed a significantly lower mean A1c (P < 0.0001) in 1493 children and youth using CSII *vs* 1846 using MDI therapy over a 5 year period in all age groups. In the T1D Exchange clinic registry, A1c was shown to be lower in CSII users *vs* MDI users (7.9% *vs* 8.5%, P < 0.001); in the longitudinal analysis, one year after initiation of CSII therapy, A1c decreased by 0.2% on average (P < 0.001), with no difference in frequency of severe hypoglycemic events (P = 0.2)[20]. Similar data have been reported in the national pediatric diabetes audit of England and Wales and in the DPV initiative of Germany and Austria at the last ISPAD meeting[21]. What is more, in their meta-analysis, Pickup and Sutton reported patients on CSII had less hyperglycemia and less severe hypoglycemia[22]. Other meta-analyses showed that the frequency of severe hypoglycemia was significantly higher with multiple daily insulin injections than with insulin-pump therapy [odds ratio (OR), OR: 4.19; 95%CI: 2.86-6.13). The greatest reduction was seen among patients who had had the greatest number of episodes of severe hypoglycemia while they were receiving injection therapy. Among these patients, the rate of severe hypoglycemia was higher by a factor of about 30 with multiple daily insulin injections than with insulin-pump therapy[16].

Finally, CSII has been associated with an improved quality of life[23,24]: CSII use is related to reduced frequency and intensity of parent stress, decreased fear of hypoglycemia, increased flexibility in quantity and timing of meals and sleep schedule, improvement in diabetes self-efficacy and independence[23,25].

However, not all children benefit from CSII. This discrepancy allows us to determine predictors for improvement of glycemic control on pump. For example, Olsen *et al*[19] showed that achievement of target A1c was significantly associated with lower A1c before insulin pump therapy initiation, younger age (< 12 years), shorter diabetes duration, higher number of daily boluses and more frequent daily self-blood glucose monitoring. Thus, patient characteristics are critical factors in deciding whether or not it is appropriate to prescribe an insulin pump to an individual.

Similar results are seen with continuous glucose monitors (CGM) use, and data from the T1D Exchange Clinic Registry showed that only a small proportion of patients with type 1 diabetes are using CGM daily in clinical practice, especially in the pediatric age range[26]. The accuracy and usability of CGM has gradually improved over the past decade so that the overall accuracy of the latest sensor generations measured as the mean relative absolute difference *vs* a given laboratory standard is in the 8%-15% range[27]. Despite this, CGM is still far from perfect. For example, more accurate evaluation of interstitial glucose levels during hypoglycemic events are necessary as CGM performs poorly in the hypoglycemic range, and the lag time between interstitial glucose and blood glucose, increased sensor sensitivity and inappropriate calibration require improvement[28].

Several studies have showed that CGM is associated with a significant reduction in A1c[29]. In two recent meta-analyses of randomized controlled trials, CGM was shown to be superior to self-monitoring of blood glucose alone in reducing A1c by almost 0.4% in both children and adults[30,31]. In a JDRF-sponsored multicenter trial, there was a larger percentage of subjects 8-14 years old using CGM who achieved at least a 10% decrease in A1c and a target A1c < 7% (59 mmol/mol), compared with children using capillary blood monitoring (SMBG)[32]. In a Cochrane meta-analysis, the largest improvement in glycemic control was observed in poorly controlled diabetes patients using CGM and CSII (sensor-augmented pump - SAP). There was no increase in risk of severe hypoglycemia or ketoacidosis in this evaluation.

Although the impact of CGM use on hypoglycemia is less clear, Floyd *et al*[31] found a significant decrease in the duration of time in both mild and severe hypoglycemia ranges and an increase in the time "in range" (70-180 mg/dL) in patient using CGM[31].

In the last few years, several studies evaluated the impact of SAP on metabolic control compared to either MDI or SMBG[33] or CSII and SMBG[34-36]. SAP therapy was demonstrated to be effective at lowering mean A1c in both adult and pediatric patients[33-36]. Switching to SAP therapy helped patients using MDI to lower their A1c levels to the same extent as the patients originally allocated to the SAP arm of the study. Benefits persisted through the entire 12-mo study phase (STAR 3 Study)[33], as well as its follow up phase[34]. Patients using SAP therapy were more likely to meet age-appropriate A1c target[33].

However, studies investigating the effectiveness of SAP in patients already using the insulin pump showed conflicting results, ranging from no significant benefit to significantly improved glycemic control[35-37].

SAP therapy was also associated with decreased time spent in hypoglycemia compared to MDI or CSII, but few significant results were found in the rate of severe hypoglycemic events.

Although current standards for diabetes management reflect the need to avoid diabetes complications, in the pediatric clinical setting, the fear of hypoglycemic events is a common barrier to achieving optimal metabolic control.

It has been reported that the most severe hypoglycemic events in children occur at night, and account for 75% of all hypoglycemic seizures[38]. Thus, children may represent a group of patients that can benefit greatly from SAP therapy, especially when a low-glucose suspend (LGS) feature is implemented (*i.e.*, the feature that automatically suspends insulin delivery when the blood glucose is less than a pre-selected value, typically 70 mg/dL). LGS and predictive low-glucose suspend (PLGS) are the first steps toward the artificial pancreas, and can help reduce family stress related to glucose management, especially overnight. LGS systems have been demonstrated to be effective in reducing the rate, severity and duration of hypoglycemia, without an increase in A1c[39]. In particular, this feature was shown to be most effective in patients with more frequent and severe hypoglycemia and in those with hypoglycemia unawareness[39].

In a study from Ly *et al*[40] the incidence of hypoglycemia after 6 mo decreased from 34.2/100 patient-months in the insulin pump group to 9.5/100 patient-months in the SAP plus LGS group, with the rate of severe hypoglycemia reduced to zero (0) in the SAP plus LGS group[39,40].

In the PLGS system, a predictive algorithm stops insulin delivery prior to reaching a predetermined threshold. Only a few outpatients studies using PLGS have been published to date, but it was shown that a further reduction of the severity of hypoglycemia as compared with SAP plus LGS alone is possible[41,42].

Despite all these encouraging results, CGM use is still difficult in youth with type 1 diabetes of all ages[43]. It is now clear that CGM can greatly help to improve glycemic control only in patients with type 1 diabetes who use the sensor for the majority of time (more than 70%)[29,31,32], and works best when used on a near-daily basis. For this reason, physical, socioeconomic and educational factors that could impact the use of this technology are an area of current research, as are predictors of pump and sensor use[44].

There are a number of barriers that may inhibit youth from wearing CGM. CGM use requires significant patient input (sensor insertion, calibration, response to sensor alarms and glucose trends) and ongoing SMBG for insulin dosing. The Juvenile Diabetes Research Foundation CGM trial on CGM satisfaction reported pain in sensor insertion, frustration with sensor alarms, skin reaction, and issues related to discomfort with wearing the device or technical problems as barriers to CGM wear[44]. In the T1D Exchange registry, CGM use was more likely in subjects with higher educational level, higher income, private insurance, longer diabetes duration and those on insulin pump[26]. In addition, recent data showed that most patients using CGM may not receive the full benefits of this technology, either because they do not use it enough or because they do not regularly download it and retrospectively review the data from the device[45].

Lack of a proper education, diminished motivation, deliberate insulin omission, and behavioral attitude can affect patients' compliance. Ensuring long-term follow-up with intensifying education and involving behavioral therapy in training might improve adherence and enhance treatment satisfaction, leading to a better glycemic control[26].

Beside technology by itself, great improvement has been observed also in immune-suppressor drugs or other drugs, useful to improve type 1 diabetes management[46].

In conclusion, since most of the recently reported epidemiological data demonstrates that a large proportion of type 1 diabetes patients do not achieve A1c targets, we consider increased education on diabetes care as a good option to improve glycemic control. New technologies may have positive outcomes, but can underperform if the technology is not used as expected[16,42-45].

While the hope for a fully automated artificial pancreas available in the near future remains, it is crucial to develop approaches for implementing and sustaining the use of technological advances that are currently available (*e.g.*, beside CSII and CGM). In addition, we need to continue our patient/family education efforts.

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