**Name of Journal: World Journal of Diabetes**

**ESPS Manuscript NO: 16649**

**Manuscript Type: EDITORIAL**

**Impact of new technologies on diabetes care**

Giani E *et al.* Impact of new technologies on diabetes care

**Elisa Giani, Andrea Enzo Scaramuzza, Gian Vincenzo Zuccotti**

**Elisa Giani, Gian Vincenzo Zuccotti,** Department of Pediatrics, Ospedale dei Bambini-V. Buzzi, Università degli Studi di Milano, 20154 Milan, Italy

**Andrea Enzo Scaramuzza,** Department of Pediatrics, Ospedale L. Sacco, 20157 Milan, Italy

**Gian Vincenzo Zuccotti,** Center for Research in Nutrition (CURN), Biomedical and Clinical Science Department, Università degli Studi di Milano, 20154 Milan, Italy

**Author contributions:** Giani E,Scaramuzza AE and Zuccotti GV developed the theme idea and performed the work, drafted the manuscript, discussed the manuscript and approved the final version of the manuscript.

**Conflict-of-interest:** the authors declare that there is no conflict of interest related to the present paper.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Gian Vincenzo Zuccotti, MD, Full Professor and Chairman,** Department of Pediatrics, Ospedale dei Bambini-V. Buzzi, Università degli Studi di Milano, 32, Via Castelvetro, 20154 Milan, Italy. gianvincenzo.zuccotti@unimi.it **Telephone:** +39-02-57995322

**Fax:** +39-02-57995132

**Received:** January 26, 2015

**Peer-review started:** January 28, 2015

**First decision:** May 14, 2015

**Revised:** May 31, 2015

**Accepted:** June 30, 2015

**Article in press:**

**Published online:**

**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

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Giani E, Scaramuzza AE, Zuccotti GV. Impact of new technologies on diabetes care. *World J Diabetes* 2015; In press

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 (EDIC) 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 (ADA) 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 and the continuous glucose monitoring 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[15]. 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 versus 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 versus 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), 4.19; 95% confidence interval (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*[20] 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 versus 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 and colleagues 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-month study phase (STAR 3 Study)[33],as well as itsfollow 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 hypoglycemia 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 JDRF 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 continuous subcutaneous insulin infusion and continuous glucose monitoring). In addition, we need to continue our patient/family education efforts.

**REFERENCES**

1 **Russell SJ**, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG, Balliro C, Hillard MA, Nathan DM, Damiano ER. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med* 2014; **371**: 313-325 [PMID: 24931572 DOI: 10.1056/NEJMoa1314474]

2 **Kovatchev BP**, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Mize LB, Farret A, Place J, Bruttomesso D, Del Favero S, Boscari F, Galasso S, Avogaro A, Magni L, Di Palma F, Toffanin C, Messori M, Dassau E, Doyle FJ. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care* 2014; **37**: 1789-1796 [PMID: 24929429 DOI: 10.2337/dc13-2076]

3 **Ly TT**, Breton MD, Keith-Hynes P, De Salvo D, Clinton P, Benassi K, Mize B, Chernavvsky D, Place J, Wilson DM, Kovatchev BP, Buckingham BA. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Care* 2014; **37**: 2310-2316 [PMID: 24879841 DOI: 10.2337/dc14-0147]

4 **Thabit H**, Lubina-Solomon A, Stadler M, Leelarathna L, Walkinshaw E, Pernet A, Allen JM, Iqbal A, Choudhary P, Kumareswaran K, Nodale M, Nisbet C, Wilinska ME, Barnard KD, Dunger DB, Heller SR, Amiel SA, Evans ML, Hovorka R. Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol* 2014; **2**: 701-709 [PMID: 24943065 DOI: 10.1016/S2213-8587(14)70114-7]

5 **Nimri R**, Muller I, Atlas E, Miller S, Fogel A, Bratina N, Kordonouri O, Battelino T, Danne T, Phillip M. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care* 2014; **37**: 3025-3032 [PMID: 25078901 DOI: 10.2337/dc14-0835]

6 **Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group**. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002; **287**: 2563-2569 [PMID: 12020338]

7 **Nathan DM**, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**: 2643-2653 [PMID: 16371630]

8 **Nathan DM**, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, Orchard TJ. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med* 2009; **169**: 1307-1316 [PMID: 19636033 DOI: 10.1001/archinternmed.2009.193]

9 **American Diabetes Association**. Standards of medical care in diabetes--2013. *Diabetes Care* 2013; **36** Suppl 1: S11-S66 [PMID: 23264422 DOI: 10.2337/dc13-S011]

10 IDF/ISPAD 2011 GLOBAL Guidelines for Diabetes in Childhood and Adolescents. Available from: URL: https://www.ispad.org/resource-type/idfispad-2011-global-guideline-diabetes-childhood-and-adolescents

11 **McKnight JA, Wild SH, Lamb MJ, Cooper MN, Jones TW, Davis EA, Hofer S, Fritsch M, Schober E, Svensson J, Almdal T, Young R, Warner JT, Delemer B, Souchon PF, Holl RW, Karges W, Kieninger DM, Tigas S, Bargiota A, Sampanis C, Cherubini V, Gesuita R, Strele I, Pildava S, Coppell KJ, Magee G, Cooper JG, Dinneen SF, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Veeze H, Aanstoot HJ, Khalangot M, Tamborlane WV, Miller KM**. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med* 2014; Epub ahead of print [PMID: 25510978 DOI: 10.1111/dme.12676]

12 **Vigersky RA**. The benefits, limitations, and cost-effectiveness of advanced technologies in the management of patients with diabetes mellitus. *J Diabetes Sci Technol* 2015; **9**: 320-330 [PMID: 25555391]

13 **Tauschmann M**, Hovorka R. Insulin pump therapy in youth with type 1 diabetes: toward closed-loop systems. *Expert Opin Drug Deliv* 2014; **11**: 943-955 [PMID: 24749563 DOI: 10.1517/17425247.2014.910192]

14 **Markowitz JT**, Harrington KR, Laffel LM. Technology to optimize pediatric diabetes management and outcomes. *Curr Diab Rep* 2013; **13**: 877-885 [PMID: 24046146 DOI: 10.1007/s11892-013-0419-3]

15 **Deeb A**, Abu-Awad S, Abood S, El-Abiary M, Al-Jubeh J, Yousef H, AbdelRahman L, Al Hajeri A, Mustafa H. Important determinants of diabetes control in insulin pump therapy in patients with type 1 diabetes mellitus. *Diabetes Technol Ther* 2015; **17**: 166-170 [PMID: 25513744 DOI: 10.1089/dia.2014.0224]

16 **Pickup JC**. Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 2012; **366**: 1616-1624 [PMID: 22533577 DOI: 10.1056/NEJMct1113948]

17 **Bruttomesso D**, Costa S, Baritussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. *Diabetes Metab Res Rev* 2009; **25**: 99-111 [PMID: 19172576 DOI: 10.1002/dmrr.931]

18 **Pańkowska E**, Błazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes* 2009; **10**: 52-58 [PMID: 18761648 DOI: 10.1111/j.1399-5448.2008.00440]

19 **Olsen B**, Johannesen J, Fredheim S, Svensson J. Insulin pump treatment; increasing prevalence, and predictors for better metabolic outcome in Danish children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2015; **16**: 256-262 [PMID: 25082292 DOI: 10.1111/pedi.12164]

20 **Blackman SM**, Raghinaru D, Adi S, Simmons JH, Ebner-Lyon L, Chase HP, Tamborlane WV, Schatz DA, Block JM, Litton JC, Raman V, Foster NC, Kollman CR, DuBose SN, Miller KM, Beck RW, DiMeglio LA. Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. *Pediatr Diabetes* 2014; **15**: 564-572 [PMID: 24494980 DOI: 10.1111/pedi.12121]

21 **Lawson ML**. Not perfect yet...but definitely better: new technology has improved diabetes care for children and adolescents (Pro Argument). ISPAD Conference 2014, 40th anniversary. Available from: URL: <https://www.ispad.org/2014/presentation/not-perfect-yetbut-definitely-better-new-technology-has-improved-diabetes-care>

22 **Pickup JC**, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008; **25**: 765-774 [PMID: 18644063 DOI: 10.1111/j.1464-5491.2008.02486.x]

23 **Müller-Godeffroy E**, Treichel S, Wagner VM. Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus--a large-scale multicentre pilot study. *Diabet Med* 2009; **26**: 493-501 [PMID: 19646189 DOI: 10.1111/j.1464-5491.2009.02707.x]

24 **Alsaleh FM**, Smith FJ, Taylor KM. Experiences of children/young people and their parents, using insulin pump therapy for the management of type 1 diabetes: qualitative review. *J Clin Pharm Ther* 2012; **37**: 140-147 [PMID: 21729118 DOI: 10.1111/j.1365-2710.2011.01283]

25 **Nuboer R**, Borsboom GJ, Zoethout JA, Koot HM, Bruining J. Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison. *Pediatr Diabetes* 2008; **9**: 291-296 [PMID: 18466210 DOI: 10.1111/j.1399-5448.2008.00396.x]

26 **Wong JC**, Foster NC, Maahs DM, Raghinaru D, Bergenstal RM, Ahmann AJ, Peters AL, Bode BW, Aleppo G, Hirsch IB, Kleis L, Chase HP, DuBose SN, Miller KM, Beck RW, Adi S. Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. *Diabetes Care* 2014; **37**: 2702-2709 [PMID: 25011947 DOI: 10.2337/dc14-0303]

27 **Mauras N**, Fox L, Englert K, Beck RW. Continuous glucose monitoring in type 1 diabetes. *Endocrine* 2013; **43**: 41-50 [PMID: 22926738 DOI: 10.1007/s12020-012-9765-1]

28 **Damiano ER**, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors. *Diabetes Care* 2013; **36**: 251-259 [PMID: 23275350 DOI: 10.2337/dc12-0070]

29 **Pickup JC**, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011; **343**: d3805 [PMID: 21737469 DOI: 10.1136/bmj.d3805]

30 **Golden SH**, Brown T, Yeh HC, Maruthur N, Ranasinghe P, Berger Z, Suh Y, Wilson LM, Haberl EB, Bass EB. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Agency for Healthcare Research and Quality (US), 2012; Report No.: 12-EHC036-EF

31 **Floyd B**, Chandra P, Hall S, Phillips C, Alema-Mensah E, Strayhorn G, Ofili EO, Umpierrez GE. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol* 2012; **6**: 1094-1102 [PMID: 23063035]

32 **Tamborlane WV**, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; **359**: 1464-1476 [PMID: 18779236 DOI: 10.1056/NEJMoa0805017]

33 **Slover RH**, Welsh JB, Criego A, Weinzimer SA, Willi SM, Wood MA, Tamborlane WV. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. *Pediatr Diabetes* 2012; **13**: 6-11 [PMID: 21722284 DOI: 10.1111/j.1399-5448.2011.00793.x]

34 **Bergenstal RM**, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Perkins BA, Welsh JB, Willi SM, Wood MA. Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. *Diabetes Care* 2011; **34**: 2403-2405 [PMID: 21933908 DOI: 10.2337/dc11-1248]

35 **Raccah D**, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, Jeandidier N, Nicolino M. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care* 2009; **32**: 2245-2250 [PMID: 19767384 DOI: 10.2337/dc09-0750]

36 **Kordonouri O**, Hartmann R, Pankowska E, Rami B, Kapellen T, Coutant R, Lange K, Danne T. Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. *Pediatr Diabetes* 2012; **13**: 515-518 [PMID: 22487079 DOI: 10.1111/j.1399-5448.2012.00863.x]

37 **Battelino T**, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, Schierloh U, Sulli N, Bolinder J. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; **55**: 3155-3162 [PMID: 22965294 DOI: 10.1007/s00125-012-2708-9]

38 **McNally K**, Rohan J, Pendley JS, Delamater A, Drotar D. Executive functioning, treatment adherence, and glycemic control in children with type 1 diabetes. *Diabetes Care* 2010; **33**: 1159-1162 [PMID: 20215458 DOI: 10.2337/dc09-2116]

39 **Bergenstal RM**, Welsh JB, Shin JJ. Threshold insulin-pump interruption to reduce hypoglycemia. *N Engl J Med* 2013; **369**: 1474 [PMID: 24106952 DOI: 10.1056/NEJMc1310365]

40 **Ly TT**, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 2013; **310**: 1240-1247 [PMID: 24065010 DOI: 10.1001/jama.2013.277818]

41 **Buckingham B**, Chase HP, Dassau E, Cobry E, Clinton P, Gage V, Caswell K, Wilkinson J, Cameron F, Lee H, Bequette BW, Doyle FJ. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Care* 2010; **33**: 1013-1017 [PMID: 20200307 DOI: 10.2337/dc09-2303]

42 **Buckingham BA**, Cameron F, Calhoun P, Maahs DM, Wilson DM, Chase HP, Bequette BW, Lum J, Sibayan J, Beck RW, Kollman C. Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. *Diabetes Technol Ther* 2013; **15**: 622-627 [PMID: 23883408 DOI: 10.1089/dia.2013.0040]

43 **Beck RW**, Hirsch IB, Laffel L, Tamborlane WV, Bode BW, Buckingham B, Chase P, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Huang ES, Kollman C, Kowalski AJ, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer SA, Wilson DM, Wolpert H, Wysocki T, Xing D. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009; **32**: 1378-1383 [PMID: 19429875 DOI: 10.2337/dc09-0108]

44 **Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group**. Validation of measures of satisfaction with and impact of continuous and conventional glucose monitoring. *Diabetes Technol Ther* 2010; **12**: 679-684 [PMID: 20799388]

45 **Liberman A**, Buckingham B, Phillip M. Diabetes technology and the human factor. *Int J Clin Pract Suppl* 2012; **175**: 79-84 [PMID: 22308993 DOI: 10.1111/j.1742-1241.2011.02858.x]

46 **Yaochite JN**, Caliari-Oliveira C, de Souza LE, Neto LS, Palma PV, Covas DT, Malmegrim KC, Voltarelli JC, Donadi EA. Therapeutic efficacy and biodistribution of allogeneic mesenchymal stem cells delivered by intrasplenic and intrapancreatic routes in streptozotocin-induced diabetic mice. *Stem Cell Res Ther* 2015; **6**: 31 [PMID: 25884215 DOI: 10.1186/s13287-015-0017-1]

**P-Reviewer:** Aureliano M, Kumar R **S-Editor:** Ji FF **L-Editor: E-Editor:**